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CLINICAL STUDY

# Effects of caffeinated coffee consumption on intraocular pressure, ocular perfusion pressure, and ocular pulse amplitude: a randomized controlled trial

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**Abstract**

***Purpose*** **To examine the effects of caffeinated coffee consumption on intraocular pressure (IOP), ocular perfusion pressure (OPP), and ocular pulse amplitude (OPA) in those with or at risk for primary open-angle glaucoma (POAG).**

***Methods*** **We conducted a prospective, double-masked, crossover, randomized controlled trial with 106 subjects: 22 with high tension POAG, 18 with normal tension POAG, 20 with ocular hypertension, 21 POAG suspects, and 25 healthy participants. Subjects ingested either 237 ml of caffeinated (182 mg caffeine) or decaffeinated (4 mg caffeine) coffee for the first visit and the alternate beverage for the second visit. Blood pressure (BP) and pascal dynamic contour tonometer measurements of IOP, OPA, and heart rate were measured before and at 60 and 90 min after coffee ingestion per visit. OPP was calculated from BP and IOP measurements. Results were analysed using paired *t*-tests. Multivariable models assessed determinants of IOP, OPP, and OPA changes.**

***Results*** **There were no significant differences in baseline IOP, OPP, and OPA between the caffeinated and decaffeinated visits. After caffeinated as compared with decaffeinated coffee ingestion, mean mm Hg changes (±SD) in IOP, OPP, and OPA were as follows: 0.99 (±1.52, $P<0.0001$), 1.57 (±6.40, $P=0.0129$), and 0.23 (±0.52, $P<0.0001$) at 60 min, respectively; and 1.06 (±1.67, $P<0.0001$), 1.26 (±6.23, $P=0.0398$), and 0.18 (±0.52, $P=0.0006$) at 90 min, respectively. Regression analyses revealed sporadic and inconsistent associations with IOP, OPP, and OPA changes.**

***Conclusion*** **Consuming one cup of caffeinated coffee (182 mg caffeine) statistically increases, but likely does not clinically impact, IOP and OPP in those with or at risk for POAG.**

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*Keywords:* caffeine; coffee; intraocular pressure; ocular perfusion pressure; ocular pulse amplitude; primary open-angle glaucoma

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## Introduction

Primary open-angle glaucoma (POAG) is the most common type of glaucoma and a major cause of blindness worldwide.[1] It is characterized by optic nerve damage, resulting in irreversible vision loss. Risk factors for the development and progression of POAG and open-angle glaucoma (OAG) include elevated intraocular pressure[2–9] (IOP) and low ocular perfusion pressure (OPP).[10–18] As IOP and OPP may be influenced by modifiable lifestyle activities,[19] identifying such factors may guide the development of preventative measures for POAG.

Caffeine consumption is a modifiable lifestyle activity that warrants investigation as it is widespread among older adults at risk for

POAG (ie, 80% of US adults >50 years old ingest caffeine daily)[20] and changing dietary habits is a relatively inexpensive measure that could prevent the development of a comparatively costly disease.[21–23] Caffeinated coffee deserves particular examination because it is the primary source of dietary caffeine and reportedly the most commonly ingested beverage wordwide.[24]

Advice regarding caffeine consumption varies because of controversy regarding the degree to which acute caffeine intake influences IOP levels. Several studies found IOP changes to be negligible,[25–30] whereas others report increases of approximately 1–4 mm Hg.[31–36]

A recent meta-analysis[37] called for more high-quality randomized clinical trials (RCTs) to better assess caffeine's effects on IOP in those with or at risk for glaucoma and in older subjects. Most RCTs investigating caffeine intake and IOP have examined healthy subjects[25,28,29,33,34] with a mean age of 25 years.[37] Only two RCTs[31,32] have enrolled glaucoma and glaucoma suspect patients, and neither disclosed the subjects' ages. Furthermore, neither trial[31,32] was participant-masked, and one study[31] was not investigator-masked.

Two trials[28,29] have investigated caffeine's effects on OPP. Although both were double-masked, only young (24–30.7 mean years old), healthy participants were enrolled. No studies have assessed caffeine's effects on ocular pulse amplitude (OPA), a surrogate of choroidal perfusion.

To the best of our knowledge, there are no prospective, double-masked RCTs that evaluate caffeine's effects on IOP, OPP, or OPA in those with or at risk for glaucoma. We report the results of a prospective, double-masked crossover RCT to assess the relationship between caffeinated coffee consumption and IOP, OPP, and OPA in patients with or at risk for POAG who are at least 40 years of age.

## Materials and methods

### *Study participants*

The study was conducted at Massachusetts Eye and Ear Infirmary (MEEI) from November 2010 to August 2011. Participants were recruited from the glaucoma and comprehensive ophthalmology clinics, and healthy subjects were additionally recruited from MEEI employees and spouses of enrolled subjects.

All participants were 40–89 years old and demonstrated in both eyes: (1) open angles on Van Herick screening or gonioscopy; and (2) slit lamp biomicroscopy showing no secondary causes of glaucoma. Subjects were excluded if they had a history of cardiac arrhythmia, liver or kidney damage, allergy to topical anaesthetic, or ocular trauma. Of the 106 participants, 103 were European-derived Caucasians and 3 were Hispanic Caucasians.

Patients were categorized into one of the five study groups: high tension POAG (HTG), normal tension POAG (NTG), POAG suspect, ocular hypertension (OHTN), and healthy. Categorization was based on visual fields (VFs), IOP history, and cup-disc ratios (CDRs). VF: Consistent with the Primary Open-Angle Glaucoma Genes and Environment Study,[38] POAG eyes demonstrated either: (A) the same glaucomatous VF defects (nasal step, nasal depression, paracentral scotoma, arcuate, or temporal wedge) on at least two reliable Humphrey VFs (HVFs); or (B) a glaucomatous VF defect on one reliable HVF with a CDR $\geq$0.7. Reliable fields had a fixation loss rate $\leq$33% and false-positive and -negative rate $\leq$20%. VF defects were either early or moderate based on the glaucoma staging system.[39] POAG suspects, OHTN, and healthy subjects demonstrated no or minimal VF defect(s) per the glaucoma staging system[39] on all available, reliable HVF(s) for both eyes. IOP HISTORY: HTG and OHTN patients had a history of IOP $\geq$22 mm Hg in at least one eye and in the study eye, whereas NTG and healthy patients had no history of IOP $\geq$22 mm Hg in both eyes. POAG suspects had no IOP restrictions. CDR: POAG suspects demonstrated a $\geq$0.7 CDR in at least one eye or $\geq$0.2 CDR asymmetry between eyes. OHTN and healthy subjects had $\leq$0.6 CDRs in both eyes and $\leq$0.1 CDR asymmetry between eyes.

One eye per patient was enrolled. Eyes were excluded if they had: (1) anterior segment laser procedure or cataract surgery in the prior 6 months; (2) glaucoma surgery; or (3) impending glaucoma laser or surgery. When both eyes of a subject were eligible, the eye with the greater CDR was selected in POAG suspects and the right eye was chosen in all other subjects.

A total of 1227 patients were screened for eligibility. In all, 963 patients were ineligible, 152 declined to participate, and 112 enrolled in the study (Figure 1). Six participants dropped out after the first study visit. Only data from the 106 participants who completed both study visits were included in the final analyses.

This study was approved by the MEEI Human Research Committee and registered on http://www.clinicaltrials.gov, identifier NCT01364207. All subjects gave written informed consent before study participation. All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed.

### *Study design*

This clinical trial was a prospective, randomized, double-masked crossover study. Enrolled study patients were

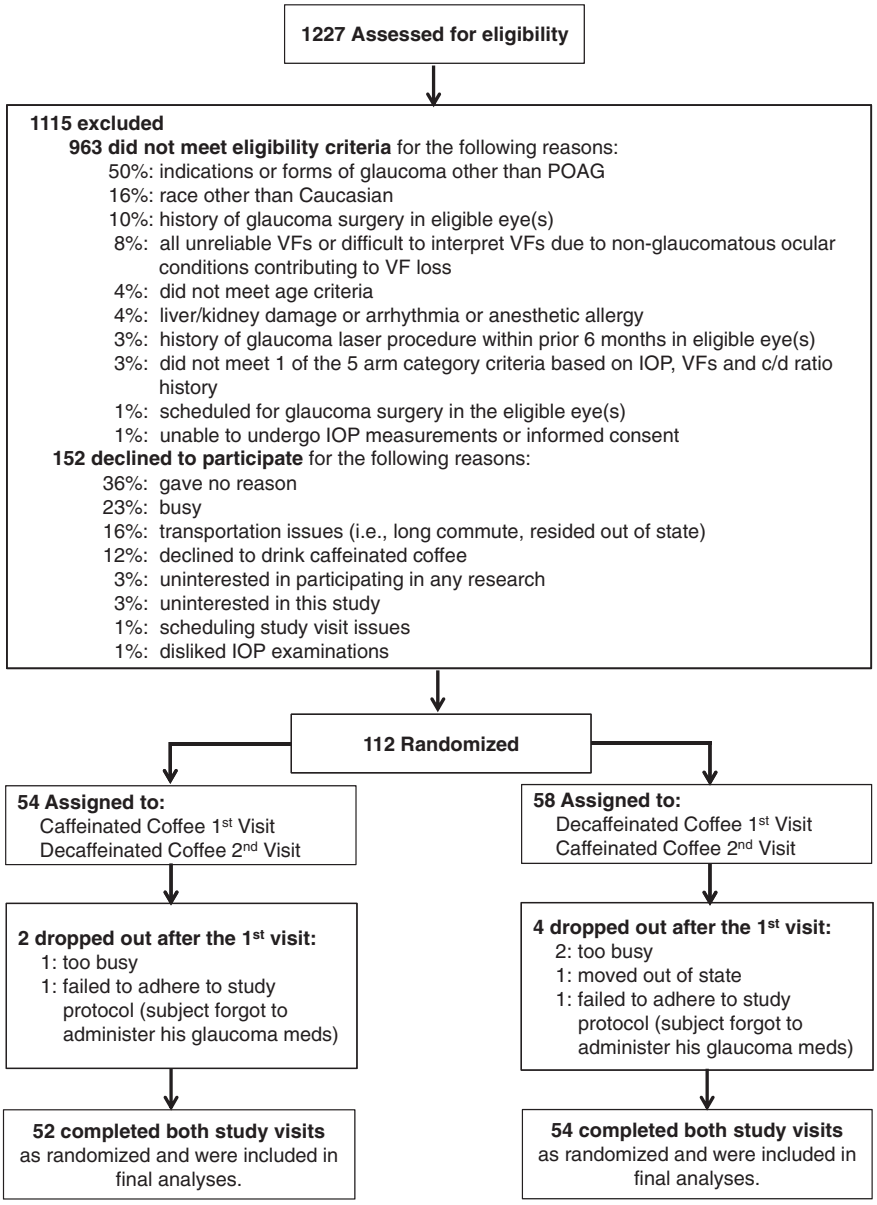


**Figure 1** Flow of participants through phases of the study.

randomized in blocks of 10 by computer-generated numbers (http://www.randomizer.org) to receive 237 ml of caffeinated or decaffeinated coffee on their first study visit and the alternate beverage on their second visit. Pharmacy staff not involved in the trial at a separate site generated and maintained the randomization list, prepared the coffee in a standardized manner, and poured the coffee into individual thermoses labelled only with the patient's initials, which were then provided to study staff. Study staff and subjects had no information regarding the content of the thermoses and were masked to subject assignment.

Harvard Biological and Chemical Laboratories (Harvard University, Cambridge, Massachusetts) determined the caffeine levels in the study coffee using liquid chromatography mass spectrometry. Each 237 ml cup of caffeinated and decaffeinated coffee contained 182 and 4 mg of caffeine, respectively, similar to caffeine levels documented in other RCTs examining coffee and IOP.[31,32]

All visits commenced between 8:00 and 10:00 hours, and each participant started each of their study visits at the same time. The second study visit was completed 2 days–4 weeks after the first. At each visit, participants ingested the coffee with 22 ml of cream in $\leq$15 min under direct study staff observation. Subjects were required to: (1) abstain from all sources of caffeine, other than the study coffee, starting at 12:01 hours the day of each visit

and ending immediately after each visit; (2) continue to take all medications including any glaucoma medications with no medication changes on and between the study visits; (3) take all morning medications at least 1 h and at the same time before each study visit; (4) abstain from fluids or foods other than the study coffee during each visit. Additionally, current smokers ($n = 6$) refrained from smoking during and at least 1 h before each visit. Compliance with these requirements was ascertained by subject self-report.

During each study visit, masked trained study staff measured IOP, OPA, heart rate (HR), and blood pressure (BP) before and 60 and 90 min after coffee ingestion, similar to time points used in other RCTs examining coffee and IOP.[31,32,34] Three quality 1 or 2 Pascal Dynamic Contour Tonometer (Ziemer Ophthalmic Systems Group Company, Port, Switzerland) measurements of IOP, OPA, and HR were taken at each time point. Two seated brachial BP measurements were taken at each time point using the digital BP monitor Omron HEM-907XL Pro (Omron Corporation, Tokyo, Japan), with a third taken if either the systolic BP (SBP) or diastolic BP (DBP) in the first two measurements differed by $>10$ mm Hg. The mean of the three IOP, OPA, HR; and 2–3 BP measurements taken per time point was used in data analyses. OPP was calculated as 2/3*[DBP + 1/3*(SBP − DBP)]–IOP.[16,18]

Subjects completed a validated questionnaire[40] regarding their daily caffeine intake. Additionally, the following was recorded for each: (1) participant—age; gender; hypertension; diabetes; family history of glaucoma in a biological parent, sibling, or child; body mass index calculated as kg/m$^2$; hypertension medications; and (2) study eye—spherical equivalent calculated as sphere + (0.5*cylinder), glaucoma laser(s), cataract surgery, glaucoma medications, and central corneal thickness as measured with a PachPen pachymeter (Accutome Inc., Malvern, PA, USA).

### *Statistical analysis*

A $P$-value $<0.05$ was statistically significant. Pooling all groups together, comparisons between the caffeinated and decaffeinated visits were analysed using paired $t$-tests. Comparisons among groups were assessed by one-way analysis of variance and $\chi^2$ test for independence. If the one-way analysis of variance tests revealed significant differences, follow-up Tukey–Kramer Multiple Comparison tests among the groups were conducted. Linear and logistic regression models assessed for determinants of IOP, OPP, and OPA changes.

For the primary hypothesis, assuming an alpha error of 5% and a power of 90%, a minimum sample size of 17 subjects per group was required to detect the smallest RCT-reported IOP change after caffeinated coffee ingestion ($\sim$1 mm Hg).[31–34]

Sample size calculations were conducted using http://www.dssresearch.com/KnowledgeCenter/toolkitcalculators/samplesizecalculators.aspx. All data analyses except regression analyses were performed using GraphPad InStat Version 3.1a (GraphPad Software Inc., La Jolla, CA, USA). Regression analyses were conducted with SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

## Results

The demographic and ocular features of the subjects who completed the trial are described in Table 1. The five groups differed significantly in terms of the percentage with a family history of glaucoma ($P = 0.0393$), percentage on glaucoma medications ($P < 0.0001$), mean number of prescribed glaucoma medications ($P < 0.0001$) and percentage with a history of glaucoma laser procedure(s) ($P < 0.0001$). The HTG group had the highest, and the healthy group generally had the lowest, percentages or numbers of these four features.

Pooling all groups together, there were no differences in baseline parameters (IOP, OPP, OPA, SBP, DBP, and HR) between the caffeinated and decaffeinated visits (Table 2). However, after caffeinated, as compared with decaffeinated, coffee ingestion all these parameters increased significantly at 60 and 90 min except for HR, which demonstrated no significant changes at both 60 and 90 min. Mean changes ($\pm$SD) in IOP, OPP, and OPA after caffeinated, as compared with decaffeinated, coffee consumption at 60 and 90 min were, respectively, in mm Hg: 0.99 ($\pm$1.52, $P < 0.0001$) and 1.06 ($\pm$1.67, $P < 0.0001$); 1.57 ($\pm$6.40, $P = 0.0129$) and 1.26 ($\pm$6.23, $P = 0.0398$); and 0.23 ($\pm$0.52, $P < 0.0001$) and 0.18 ($\pm$0.52, $P = 0.0006$). Comparison of the changes in IOP, OPP, OPA, SBP, DBP, and HR at 60 *vs* 90 min after caffeinated, as compared with decaffeinated, coffee intake revealed no statistically significant differences (data not shown).

We compared IOP, OPP, and OPA between the five groups (Table 3). At baseline, each of these parameters differed significantly between the groups. However, the changes in these parameters generally did not differ significantly between the five groups after caffeinated, as compared with decaffeinated, coffee ingestion at 60 and 90 min. The exception was the change in IOP at 60 min ($\pm$SD) in mm Hg: the HTG group demonstrated a significantly smaller change (0.19 $\pm$1.09) compared with the POAG suspect (1.51 $\pm$1.53, $P < 0.05$) and OHTN (1.61 $\pm$1.85, $P < 0.05$) groups.

We examined each of the 106 participants' changes in IOP, OPP, and OPA at 90 min after caffeinated, as compared with decaffeinated, coffee consumption. With respect to $\Delta$IOP in mm Hg, 33 subjects had $\geq +2$, 71

**Table 1** Demographic and ocular features of study participants

| | *All participants* | *HTG* | *NTG* | *POAG suspect* | *OHTN* | *Healthy* | P *value* |
|---|---|---|---|---|---|---|---|
| *N* | 106 | 22 | 18 | 21 | 20 | 25 | |
| Age, mean (SD), years | 64.4 (11.7) | 66.5 (9.0) | 69.1 (10.9) | 64.8 (13.9) | 62.7 (10.1) | 60.0 (12.9) | 0.11 |
| Gender, % male | 49.1 | 59.1 | 44.4 | 52.4 | 45 | 44 | 0.83 |
| Famliy history of glaucoma, % | 40.6 | 63.6 | 33.3 | 47.6 | 40.0 | 20.0 | 0.0393 |
| BMI, mean (SD), kg/m$^2$ | 26.6 (5.1) | 28.2 (5.1) | 26.1 (7.2) | 25.0 (3.4) | 27.6 (5.4) | 26.0 (4.0) | 0.23 |
| Hypertension, % | 51.9 | 59.1 | 61.1 | 42.9 | 50.0 | 48.0 | 0.75 |
| No. of hypertension medications, mean (SD) | 0.8 (0.9) | 0.8 (0.8) | 1.0 (1.0) | 0.7 (1.0) | 0.8 (0.9) | 0.8 (0.9) | 0.84 |
| Diabetes mellitus, % | 4.7 | 9.1 | 0.0 | 14.3 | 0.0 | 0.0 | 0.08 |
| Current smoking, % | 5.7 | 0.0 | 11.1 | 0.0 | 15.0 | 4.0 | 0.14 |
| Caffeine/day, mean (SD), mg | 260.5 (296.2) | 208.9 (194.6) | 268.2 (203.3) | 241.4 (217.7) | 349.7 (520.4) | 245.0 (240.2) | 0.63 |
| CCT, mean (SD), $\mu$ | 548.7 (41.1) | 542.2 (25.9) | 535.4 (28.0) | 549.8 (52.4) | 559.7 (47.3) | 554.2 (43.2) | 0.37 |
| Spherical equivalent[a], mean (SD), dioptres | −1.1 (2.8) | −0.9 (2.6) | −1.2 (2.6) | −1.4 (2.8) | −0.9 (3.4) | −1.0 (2.9) | 0.97 |
| Glaucoma medications, % | 54.7 | 100.0 | 94.4 | 33.3 | 60.0 | 0.0 | <0.0001 |
| No. of glaucoma medications, mean (SD) | 1.0 (1.2) | 2.4 (1.0) | 1.6 (0.9) | 0.6 (1.0) | 0.9 (0.9) | 0.0 (0.0) | <0.0001 |
| Glaucoma laser, % | 11.3 | 40.9 | 11.1 | 0.0 | 5.0 | 0.0 | <0.0001 |
| Cataract surgery, % | 17.9 | 31.8 | 27.8 | 9.5 | 5.0 | 8.0 | 0.09 |

Abbreviations: HTG, high tension POAG; NTG, normal tension POAG; OHTN, ocular hypertension; BMI, body mass index; CCT, central corneal thickness.
[a]Spherical equivalent calculated as sphere + (0.5 * cylinder).

**Table 2** Changes in various parameters before and after coffee ingestion for all participants

| | *Mean (SD),* n = *106* | | | P *value* |
|---|---|---|---|---|
| | *Caffeinated visit* | *Decaffeinated visit* | *Caffeinated visit minus decaffeinated visit* | |
| *IOP* | | | | |
| Baseline | 15.90 (2.78) | 16.01 (2.72) | −0.11 (1.50) | 0.4436 |
| Δ At 60 min | 1.51 (1.54) | 0.52 (1.29) | 0.99 (1.52) | <0.0001 |
| Δ At 90 min | 1.46 (1.68) | 0.40 (1.37) | 1.06 (1.67) | <0.0001 |
| *OPP* | | | | |
| Baseline | 42.10 (7.59) | 42.05 (7.09) | 0.04 (4.83) | 0.9294 |
| Δ At 60 min | 2.23 (5.07) | 0.66 (5.03) | 1.57 (6.40) | 0.0129 |
| Δ At 90 min | 2.50 (5.35) | 1.24 (4.78) | 1.26 (6.23) | 0.0398 |
| *OPA* | | | | |
| Baseline | 2.49 (1.05) | 2.44 (0.96) | 0.05 (0.50) | 0.2985 |
| Δ At 60 min | 0.45 (0.44) | 0.22 (0.34) | 0.23 (0.52) | <0.0001 |
| Δ At 90 min | 0.38 (0.45) | 0.20 (0.38) | 0.18 (0.52) | 0.0006 |
| *SBP* | | | | |
| Baseline | 120.11 (16.81) | 120.38 (15.24) | −0.27 (11.24) | 0.8054 |
| Δ At 60 min | 7.34 (11.28) | 2.29 (10.74) | 5.05 (14.35) | 0.0004 |
| Δ At 90 min | 7.68 (12.12) | 2.39 (10.07) | 5.29 (12.58) | <0.0001 |
| *DBP* | | | | |
| Baseline | 70.44 (11.33) | 70.46 (10.93) | −0.02 (6.68) | 0.9720 |
| Δ At 60 min | 4.75 (7.38) | 1.51 (7.15) | 3.24 (8.87) | 0.0003 |
| Δ At 90 min | 5.07 (7.44) | 2.50 (6.96) | 2.57 (9.65) | 0.0071 |
| *HR* | | | | |
| Baseline | 64.84 (10.14) | 65.60 (10.20) | −0.76 (5.89) | 0.1868 |
| Δ At 60 min | −3.79 (4.94) | −2.89 (4.04) | −0.91 (5.16) | 0.0730 |
| Δ At 90 min | −3.78 (5.21) | −3.34 (4.29) | −0.44 (5.24) | 0.3854 |

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; IOP, intraocular pressure; OPA, ocular pulse amplitude; OPP, ocular perfusion pressure; SBP, systolic blood pressure.
All units in mm Hg except HR (beats/min).

had between +2 and −2, and 2 had ≤ −2. In terms of ΔOPP in mm Hg, 7 participants had ≥ +10, 94 had between +10 and −10, and 5 had ≤ −10. With regards to ΔOPA in mm Hg, 7 subjects had ≥ +1, 96 had between +1 and −1, and 3 had ≤ −1. Of the participants with ΔIOP ≥ +2 mm Hg, five also demonstrated ΔOPP ≤ −5 mm Hg and zero demonstrated ΔOPP ≤ −10 mm Hg. The 60 min results are similar.

Multiple linear and logistic regression models (data not shown) assessed determinants of IOP, OPP, and OPA changes at 60 and 90 min. There were no consistently statistically significant associations between any of the covariates of interest (age, gender, body mass index, hypertension, diabetes, glaucoma status, family history of glaucoma, baseline IOP, daily caffeine intake) and outcome parameters.

## Discussion

In this double-masked crossover RCT, we demonstrated that consuming 237 ml of caffeinated, as compared with decaffeinated, coffee significantly increases, at 60 and 90 min: IOP by ~1 mm Hg, OPP by ~1.25–1.50 mm Hg, and OPA by ~0.2 mm Hg. On average, the small increase in IOP was offset by an increase in OPP of similar magnitude. These one-time, modest and presumably transient increases in IOP and OPP are unlikely to impact conversion to or progression of glaucoma. However, a small minority of subjects demonstrated larger and

**Table 3** Comparison of changes in IOP, OPP, and OPA between groups

| | *Mean (SD)* | | | | | P *value* |
|---|---|---|---|---|---|---|
| | *HTG* | *NTG* | *POAG Suspect* | *OHTN* | *Healthy* | |
| *N* | 22 | 18 | 21 | 20 | 25 | |
| *IOP* | | | | | | |
| Baseline[a] | 15.98 (2.71) | 14.12 (1.82) | 16.76 (2.84) | 17.37 (2.39) | 15.45 (2.37) | 0.0011[b] |
| Δ At 60 $\text{min}_{\text{caffeinated visit minus decaffeinated visit}}$ | 0.19 (1.09) | 0.94 (1.23) | 1.51 (1.53) | 1.61 (1.85) | 0.81 (1.46) | 0.0134[c] |
| Δ At 90 $\text{min}_{\text{caffeinated visit minus decaffeinated visit}}$ | 0.68 (1.11) | 1.44 (1.61) | 1.48 (1.74) | 0.84 (1.88) | 0.95 (1.89) | 0.4387 |
| *OPP* | | | | | | |
| Baseline | 45.57 (5.21) | 41.12 (6.44) | 41.15 (6.64) | 37.73 (6.48) | 43.94 (7.45) | 0.0021[d] |
| Δ At 60 $\text{min}_{\text{caffeinated visit minus decaffeinated visit}}$ | 1.44 (7.17) | 2.43 (7.68) | 0.53 (5.02) | 2.02 (6.26) | 1.58 (6.22) | 0.9155 |
| Δ At 90 $\text{min}_{\text{caffeinated visit minus decaffeinated visit}}$ | − 0.26 (6.32) | 2.90 (6.15) | 0.05 (6.70) | 2.18 (5.51) | 1.69 (6.33) | 0.4232 |
| *OPA* | | | | | | |
| Baseline | 2.29 (0.95) | 1.91 (0.77) | 2.70 (1.02) | 2.71 (0.86) | 2.61 (1.05) | 0.0456[e] |
| Δ At 60 $\text{min}_{\text{caffeinated visit minus decaffeinated visit}}$ | 0.05 (0.52) | 0.32 (0.45) | 0.22 (0.50) | 0.34 (0.54) | 0.23 (0.55) | 0.3899 |
| Δ at 90 $\text{min}_{\text{caffeinated visit minus decaffeinated visit}}$ | 0.05 (0.38) | 0.36 (0.46) | 0.17 (0.48) | 0.20 (0.63) | 0.15 (0.59) | 0.4834 |

Abbreviations: HTG, high tension POAG; IOP, intraocular pressure; NTG, normal tension POAG; OHTN, ocular hypertension; OPA, ocular pulse amplitude; OPP, ocular perfusion pressure.
All units in mm Hg.
[a] Baseline calculated as the average of the caffeinated and decaffeinated visit baseline values before beverage consumption.
[b] NTG *vs* POAG suspect $P<0.05$, NTG *vs* OHTN $P<0.001$.
[c] HTG *vs* POAG suspect $P<0.05$, HTG *vs* OHTN $P<0.05$.
[d] OHTN *vs* HTG $P<0.01$, OHTN *vs* healthy $P<0.05$.
[e] Although the one-way ANOVA reveals a *P*-value of $<0.05$, the subsequent Tukey–Kramer multiple comparisons post-tests reveal no statistically significant differences between the arms.

potentially clinically significant increases in IOP or decreases in OPP after caffeinated, as compared with decaffeinated, coffee consumption. Our multivariate analyses, which may be underpowered, failed to reveal consistently significant determinants of changes in IOP, OPP, or OPA. Also, owing to the few studies examining OPA and clinical outcomes,[41,42] it is unclear whether the OPA changes observed in our trial are clinically significant. However, the absence of a decrease in OPA, within the context of slight increases in IOP and OPP, is consistent with our overall results.

Our IOP findings are consistent with those reported in Higginbotham *et al*[32] who examined glaucoma and glaucoma suspect subjects in an investigator-masked RCT and also found a statistically but not clinically significant IOP elevation after caffeinated coffee consumption. Our OPP results differ from those reported in two double-masked studies, which found no change in OPP after caffeine tablet ingestion in 10 or 14 young (age range 20–44 years), healthy subjects.[28,29] However, these two studies may be underpowered to detect a statistically significant change in OPP and the studies' results may not be generalized to older patients and those with or at risk for glaucoma. Although no prior studies have investigated the effects of caffeine consumption on OPA, our baseline OPA results are consistent with previous reports.[41–43] Our SBP and DBP increases are consistent with the BP changes after acute caffeine intake documented in the literature.[29,31,32,34,44] Our HR results are consistent with those reported in other RCTs investigating the effects of acute caffeine intake.[28,29,32]

Caffeine may increase IOP through several possible mechanisms. First, as a phosphodiesterase inhibitor, caffeine increases intracellular cyclic AMP,[45] which may increase aqueous humour (AqH) formation. However, evidence suggests that inhibition of phosphodiesterase activity does not occur with the caffeine blood levels achieved from 2–3 cups of coffee.[46] Second, one investigator theorized[34] that caffeine's adenosine receptor antagonist effect could inhibit AqH outflow by decreasing smooth muscle tone in the filtration apparatus, leading to trabecular fenestrae closure. However, Kurata *et al*[47] demonstrated in beagle dogs that caffeine's IOP elevating effects may be due to increased AqH formation and not through the inhibition of AqH drainage through the trabecular meshwork. Third, caffeine's adenosine receptor blockade[46,48,49] is thought to be responsible for caffeine's well-known BP-elevating effect,[50–53] which could increase the hydrostatic pressure for AqH formation. In rats intravenously injected with caffeine, ultrastructural changes in the non-pigmented ciliary epithelium were observed, suggesting AqH transportation enhancement.[54] Additionally, acute caffeine may increase BP before causing IOP elevations.[34]

Although our study was not designed to determine the mechanism of IOP change after caffeine consumption, the increases in SBP, DBP, and OPP we observed lend support to the third proposed mechanism. It is possible that caffeine may increase OPP and OPA also through the inhibition of adenosine receptors, resulting in reduced vasodilation and increased BP.

Our study has several strengths. It is the largest RCT to investigate the relationship between caffeine intake and IOP. It is also the first double-masked RCT that examines IOP, and the first study to assess OPP, after caffeine intake in those with or at risk of glaucoma. It is also the first trial to examine OPA after caffeine consumption. Other strengths include the wider 40–89-year-old age range and older 64-year-old mean age of our subjects, compared with the 20–44-year-old age range and approximately 25 year mean age of subjects in the other trials combined,[25,28,29,33,34,37] as the risk of POAG increases after age 40. The study's crossover design minimized individual variations, enhancing its power. Unlike other RCTs, we did not exclude subjects on antiglaucoma medications,[25,28,29,31,33,34] on systemic medications,[25,31] with a history of cataract surgery or glaucoma laser procedure before the 6 months preceding the study,[25,28,31–34] with systemic hypertension,[25,29,31,34] with diabetes,[25,29] who currently smoke,[29,33] who have a family history of glaucoma[33,34] and who ingest beyond a certain daily level of caffeine.[25,29] The absence of these exclusions enhanced the generalizability of our results.

Our study has some limitations. We did not determine the full duration of the IOP, OPP, and OPA elevations observed in our trial. Owing to feasibility concerns regarding the participants' time constraints, our study's time frame was limited to 90 min after coffee ingestion, similar to or longer than the time frames employed by most RCTs examining caffeine consumption and IOP.[25,29,31,32,34] Our findings of statistically significant increases in IOP, OPP,and OPA at 60 and 90 min, as well as no significant differences in the changes in outcome parameters at 60 *vs* 90 min, suggest that the outcome parameter elevations may have continued beyond 1.5 h. Our results are consistent with those reported in Avisar *et al*[31] and Higginbotham *et al*,[32] who both demonstrated statistically significant IOP elevations at 90 min after caffeinated coffee intake but did not monitor IOP beyond this time point. Adams and Brubaker[55] found no significant difference in IOP 4 h after caffeine ingestion, suggesting that caffeine's effects on IOP is transient. Caffeine levels generally peak 30–120 min after oral intake and caffeine's half-life is 3–6 h.[44] Caffeine's BP-elevating effects typically occur within 30 min, peak in 1–2 h and may persist for more than 4 h.[44] Thus, the outcome parameters increases observed in our trial possibly persisted beyond 1.5 h and declined to baseline within hours afterwards.

Other limitations of our study include our eligibility criteria. Our results may not be applicable to non-Caucasians; those with secondary glaucoma or glaucoma surgery; eyes with advanced glaucoma; those non-adherent with their glaucoma medications; and those with impending glaucoma laser or surgery.

Further investigation into the determinants of IOP, OPP, and OPA changes after caffeine intake is warranted, as caffeine may not be recommended for the minority of our study subjects who demonstrated potentially clinically significant changes in outcome parameters. More work is needed to elucidate the duration of outcome measure changes from one cup of coffee. Future trials can investigate the possibility that repeated exposure to caffeine throughout the day may cause sustained, clinically significant changes in IOP, OPP, and OPA in those with or at risk for glaucoma. The average American daily coffee consumption is about 3.5 cups[56] and no trials have examined repeated acute caffeine ingestion in those with or at risk for glaucoma. Okimi *et al*[33] did demonstrate that IOP levels were statistically increased at 3 h after young, healthy participants ingested four cups of caffeinated coffee within an hour. However, consuming 946 ml of coffee within 60 min likely does not mimic the drinking habits of the average person, and the study's results may not be applicable to older patients or those with or at risk for glaucoma. Additionally, coffee consumption has been associated with elevated IOP in OAG patients in a cross-sectional study.[57] Kang *et al*[58] found that caffeine intake may be a risk factor for incident HTG for those with a family history of glaucoma. Our study did not find that the ingestion of one cup of caffeinated coffee adversely effected IOP, OPP, or OPA among participants with a family history of glaucoma. Perhaps, a larger sample size and/or a higher level of caffeinated coffee consumption are needed to observe such effects.

We exposed subjects to caffeinated coffee to replicate realistic and clinically relevant scenarios. Our study was not designed or able to assess which caffeinated coffee components were responsible for the outcome parameter changes we observed. Non-caffeine components of caffeinated coffee could contribute to the IOP effects we report. In fact, negligible changes in IOP were found in three trials examining oral caffeine (*vs* placebo) tablets in healthy subjects[25,28,29] and in a study investigating the effects of caffeine topical drops in five subjects.[30] Thus, as Li *et al*[37] noted, more study of the mechanism by which caffeine mediates its effects on ocular parameters is needed.

In summary, in this first double-masked RCT assessing IOP, OPP, and OPA after caffeinated coffee consumption in those with or at risk for POAG, we found that one cup of caffeinated (182 mg caffeine), as compared with

decaffeinated (4 mg caffeine), coffee statistically increases but likely does not clinically impact IOP or OPP for the majority of study participants.

**Summary**

**What was known before**

- Several studies found IOP changes after acute caffeine intake to be negligible, whereas others report increases of ~1–4 mm Hg.
- Two double-masked randomized controlled trials (RCTs) found no change in OPP after caffeine tablet ingestion in 10 or 14 young, healthy subjects.
- No studies have assessed caffeine's effects on OPA, a surrogate of choroidal perfusion.

**What this study adds**

- Our study is the largest RCT to investigate the relationship between caffeine intake and IOP. It is also the first double-masked RCT that examines IOP, and the first study to assess OPP, after caffeine intake in those with or at risk for glaucoma. It is also the first trial to examine OPA after caffeine consumption.
- We demonstrated that consuming 237 ml of caffeinated, as compared with decaffeinated, coffee statistically significantly increases on average, at 60 and 90 min: IOP by ~1 mm Hg, OPP mean by ~1.25–1.50 mm Hg, and OPA by ~0.2 mm Hg. These one-time modest and presumably transient changes are unlikely to be clinically significant.

## Conflict of interest

The authors declare no conflict of interest.

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