

Effects of Caffeine on Microcirculation of the Human Ocular Fundus

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Purpose: To determine the effect of caffeine on microcirculation in the human ocular fundus.

Methods: The microcirculation in the ocular fundus of 10 healthy volunteers (10 eyes) was studied using a laser speckle tissue circulation analyzer. Caffeine or placebo (100 mg) was administered orally in a double-masked manner. Square blur rate (SBR), a quantitative index of blood flow velocity, was measured in a temporal site of the optic nerve head (ONH) free of surface vessels and in a middle site of the choroid-retina between the ONH and macula. Intraocular pressure (IOP), blood pressure (BP), pulse rate (PR), and central critical fusion frequency (CFF) were also measured. These parameters were measured before and for 2 hours after administration. The area under curve (AUC) of SBR was calculated for each area. Ocular perfusion pressure (OPP) was also calculated from BP and IOP.

Results: The time-course of change in SBR value showed much individual difference. Caffeine decreased the AUC of SBR in the ONH ($P = .0218$) as well as in the choroid-retina ($P = .0469$) significantly. IOP, mean BP, PR, OPP, and central CFF did not change significantly.

Conclusions: These results suggest that caffeine may increase blood vessel resistance and decrease blood flow in the human ONH and choroid-retina. **Jpn J Ophthalmol 2002;46:170-176** © 2002 Japanese Ophthalmological Society

Key Words: Caffeine, capillary blood flow of optic nerve head, choroid-retinal circulation, human eye, laser speckle method.

Introduction

In addition to intraocular pressure (IOP), ocular blood flow has also recently been shown to play a role in the development and progression of glaucoma.¹⁻⁵ Interest is now being focused on how this affects the microcirculation of the optic nerve head (ONH). The recent heightened interest in general health maintenance has also led to a growing interest in the effects of food products such as coffee and tea. Research on the effects of caffeine on blood circulation has demonstrated a decrease in cerebral blood flow.⁶⁻⁸ Studies of the relationship between caffeine and ocular blood flow have thus far been limited to

investigation by blue field entoptoscopy of the effects on macular blood flow.⁹ There have been no reports concerning caffeine ingestion and its effects on serial changes in ONH microcirculation. Therefore, in the present study, we used the laser speckle method to evaluate the effects of caffeine ingestion on human ocular microcirculation.

Materials and Methods

The subjects in this study were 10 healthy volunteers (10 eyes) without any ophthalmologic disorders (other than simple myopia), and comprised 5 men and 5 women ranging in age from 25 to 44 years (mean \pm SD, 30.7 \pm 6.4 years). Caffeine ingestion, food and drink of any kind, and exercise were prohibited for 6 hours, 2 hours, and 30 minutes before testing, respectively. The study was conducted in a double-blind manner. All subjects underwent the same experimental procedure.

Received: April 6, 2001

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During the study period, each subject was examined at 1-week intervals and given a capsule containing either 100 mg caffeine or 100 mg lactose (as the control) before the testing. To minimize any diurnal variation effects, testing was conducted at the same time each day. This research study was approved by the Ethics Committee at Osaka Medical College. The nature of the study was explained to each subject, and consent was obtained prior to participation.

At each weekly examination, after the administration of one drop of 0.4% tropicamide (Mydrin M[®], Santen, Osaka) for mydriasis, a photograph of the ocular fundus was taken in order to decide each measurement area. The ONH and choroid-retina square blur rate values (SBR value), blood pressure, and IOP were measured before and after the oral administration of caffeine or placebo at 15-minute intervals afterward for up to 2 hours. The central critical fusion frequency (CFF) was also measured before and after treatment at 30-minute intervals for up to 2 hours. The each subject, the eye in which measurements were performed was randomly selected, but this same eye was always used in the caffeine and control experiments. The image speckles from a field located in the temporal ONH, and those from a field between the macula and the ONH, free of surface vessels, were recorded for measurement of the SBR values in the ONH and in the choroid-retina, respectively. The SBR values in the ONH and in the choroid-retina were calculated and averaged for 5 cardiac cycles to obtain the mean SBR values.

The mechanism of the laser speckle tissue circulation analyzer has been described in other reports.¹⁰⁻¹⁵ The system consists of a fundus camera (TRC-WT3[®], Topcon, Tokyo) equipped with a diode laser (wavelength = 808 nm). The scattered laser light is imaged on a sensor (100 × 100 pixels, BASIS type, Canon, Tokyo) and corresponds to the 0.72 × 0.72 mm field (45° visual angle) in the human fundus where the speckle pattern appears. The normalized blur (NB) is an approximation of the reciprocal of speckle contrast due to the interference phenomenon when laser light is scattered by the retina. This value serves as an indicator of blood flow velocity. The SBR correlates with the square of the NB, and, in measurements of high flow velocity, it shows a more linear correlation with velocity than does the NB.^{14,15}

The SBR is a relative index of blood flow velocity. Evaluation of the SBR does not involve measurement of actual values. Relative SBR values are calculated as ratios of the value obtained prior to administration of the caffeine or placebo.

The area under the curve (AUC)¹⁶ is an integrated

value based on sequential changes. It is positive when the relative SBR is greater than 1 and negative when the relative SBR is less than 1. The AUC for the SBR values of the ONH and choroid-retina in each subject were calculated up to 2 hours after administration of caffeine or placebo.

Brachial arterial blood pressure and pulse rate were measured using an automated sphygmomanometer (JENTOW-7700[CS]; Nippon Colin, Komaki), after the determination of SBR values by the laser speckle method. Mean blood pressure (BPm) was calculated from systolic blood pressure (BPs) and diastolic blood pressure (BPd), according to the following equation:

$$\text{BPm} = \text{BPd} + 1/3(\text{BPs} - \text{BPd})$$

IOP was also measured with a Goldmann applanation tonometer after determination of the SBR value of the ONH. Using the above values of IOP and BPm, OPP was calculated using the following equation:

$$\text{OPP} = 2/3\text{BPm} - \text{IOP}$$

Measurement of the central CFF was performed using a central CFF-meter (Yagami, Nagoya).

For statistical analysis, analysis of variance and multiplicity were performed for each measured value, and comparisons with control values were made using a paired *t*-test with Bonferroni's correction. The AUC data was analyzed as a nonparametric variable using the Wilcoxon signed-rank test.

Results

Figure 1 shows the relative SBR values (ie, sequential changes in relative SBR values), compared to values obtained before the administration of caffeine or placebo (Figure 1A, in ONH; Figure 1B, in choroid-retina). The relative SBR values in the ONH were lowest from 45 to 60 minutes after administration. The values decreased from the baseline (before administration) by 10% at 45 minutes and by 8% at 60 minutes. Analysis of the data at 60 minutes by paired *t*-test with Bonferroni's correction showed a significant difference between caffeine and the control substance ($P = .0264$). The relative SBR values in the choroid-retina tended to decrease from 45 to 75 minutes after administration with a 6% decrease at 60 minutes, although *P* values were more than 0.1 during this period.

Figure 2 shows the distribution of times for lowest SBR values after the administration of caffeine (Figure 2A, in ONH; Figure 2B, in choroid-retina). There were variations in both sites; these variations were particularly prominent in the choroid-retina.

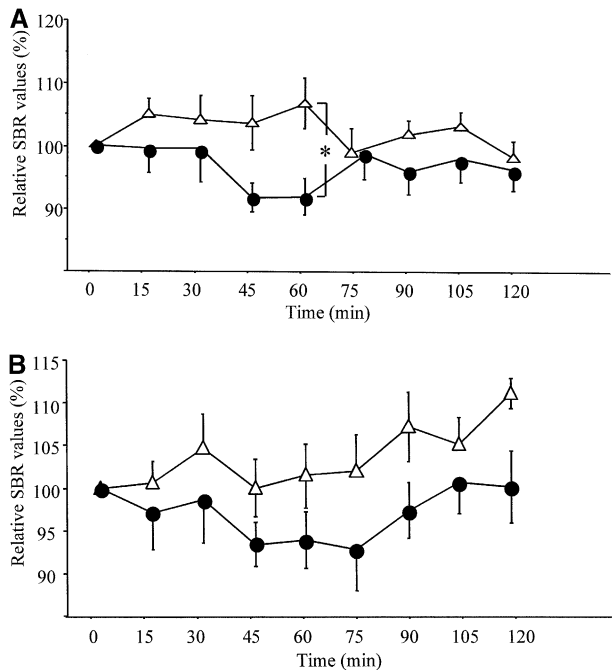


Figure 1. Sequential changes in relative square blur rate (SBR) values. (A) Optic nerve head, (B) choroid-retina. Relative SBR value is calculated as ratio of value obtained prior to administration of caffeine (●) or placebo (Δ) ($n = 10$, mean \pm SE). (A) $*P < .05$ (paired t -test with Bonferroni's correction). There are no significant differences between effects of caffeine and placebo ($P = .069$, repeated-measures analysis of variance [ANOVA]). (B) There are no significant differences between caffeine and placebo ($P > .10$, repeated-measures ANOVA).

Figure 3 shows the AUC for the SBR values after caffeine or placebo (Figure 3A, in ONH; Figure 3B, in choroid-retina). In both the ONH and choroid-retina, data analysis by the Wilcoxon signed-rank test showed significant differences in the data for caffeine and the placebo ($P = .0218$, $P = .0469$, respectively).

Table 1 lists the changes in mean blood pressure, IOP, OPP, pulse rate, and central CFF after the administration of caffeine or placebo. There were no significant differences in these data between caffeine and the placebo.

Discussion

Whether patients with glaucoma should consume products containing caffeine is still a matter of debate. Some investigators have shown that caffeine increases IOP, and recommended that it be avoided.^{17,18} Other studies have shown that ingestion of as much as 400 mg of caffeine does not raise IOP in normal volunteers.¹⁹ Recently, ONH microcirculation, in addition

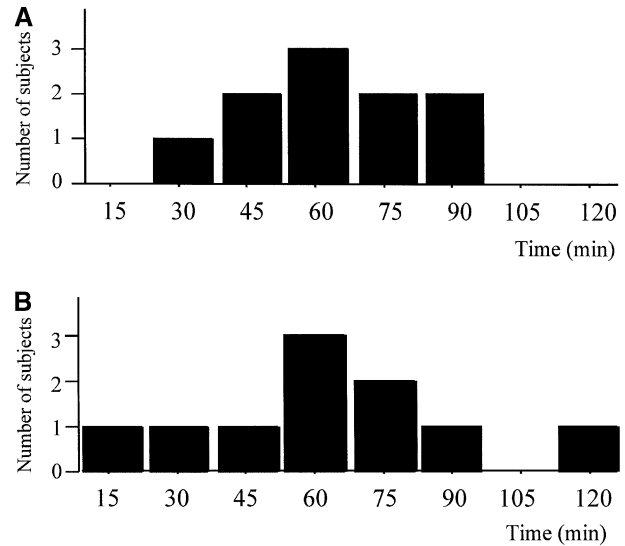


Figure 2. Distribution of lowest square blur rate values after administration of caffeine. (A) Optic nerve head, (B) choroid-retina. $n = 10$, mean \pm SE.

to IOP, has been shown to be a factor in the development of glaucoma. No previous studies have investigated the effects of caffeine on ONH microcirculation. Therefore, the present study evaluated these effects in normal healthy volunteers.

Caffeine is a common ingredient in many popular beverages, such as green tea, black tea, oolong tea, and coffee. One cup (140 mL) of one of these beverages may contain from 20 to 146 mg of caffeine.²⁰ Blood concentrations of caffeine generally reach peak values about 30 to 90 minutes after ingestion. The blood half-life varies from 2 to 10 hours.²¹⁻²⁶ The systemic effects of caffeine have been reported elsewhere in detail. Caffeine generally produces a maximum rise in blood pressure about 15 to 90 minutes after ingestion. This effect may persist for 3 to 4 hours.^{21,23-25} The effect of caffeine on heart rate varies among individuals. Some people develop tachycardia,^{9,23,25} whereas others may develop bradycardia²⁷ due to a vagal response to a rise in blood pressure.

Several studies have also investigated the effects of caffeine on blood flow. Measurements using a thermoelectric flow recorder have shown that intravenous administration of 500 mg caffeine decreases cerebral blood flow.⁶ Measurements taken using a ¹³³Xenon inhalation technique have shown that oral administration of 250 mg or 500 mg of caffeine decreases regional cerebral blood flow 30 minutes after ingestion.⁷ A more recent study using positron emission tomography (PET) reported an approximately 30% decrease in cerebral blood flow (30 minutes) af-

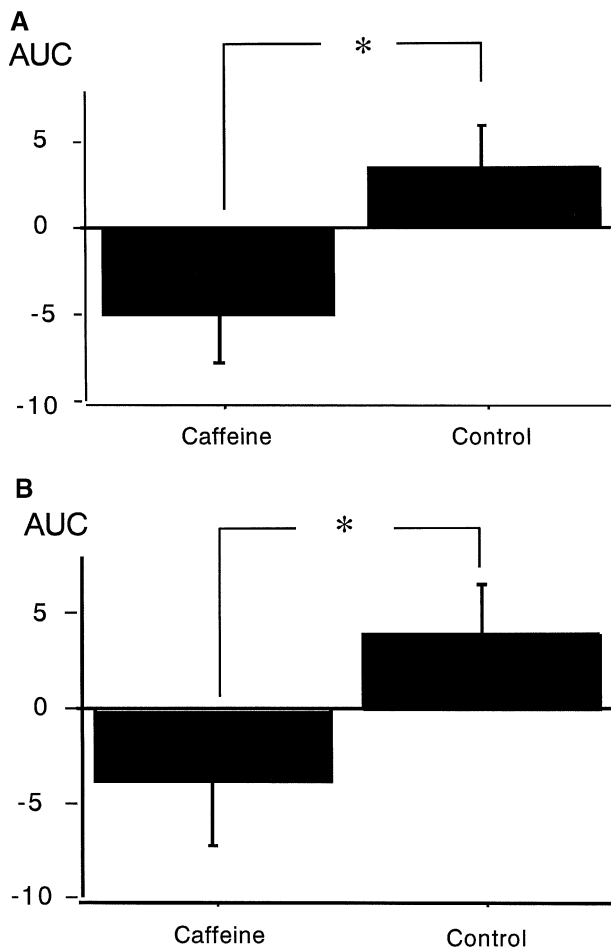


Figure 3. Area under curve (AUC) for square blur rate values after administration of caffeine or placebo. (A) Optic nerve head, (B) choroid-retina. $n = 10$, mean \pm SE. * $P < .05$ (Wilcoxon signed ranks test).

ter oral administration of 250 mg caffeine.⁸ These studies demonstrate that caffeine often causes a decrease in cerebral blood flow. On the other hand, cerebral blood flow in neonates may not decrease. One study using measurements by Doppler ultrasound reported no changes after intravenous administration of 20 mg/kg of caffeine citrate,^{28,29} and another study using measurement by a Xenon clearance technique reported an actual increase in blood flow compared to control.³⁰ A study using dynamic PET to measure coronary artery blood flow after ingestion of 1 to 2 cups of coffee reported an increase in vascular resistance at rest but no significant changes in blood flow.³¹ However, increased blood flow due to administration of dipyridamole was significantly inhibited.³¹ Another study reported that ingestion of 2 cups of coffee during the last trimester of pregnancy

decreased placental blood flow, but there was no change in umbilical vein blood flow.³² An investigation of the effects of caffeine on mesenteric artery blood flow showed a slight decrease in young healthy control subjects.³³ A study of neonates, using Doppler ultrasound measurements, found that caffeine did produce a decrease in mesenteric artery blood flow.³⁴ In summary, many studies have investigated the effects of caffeine on blood flow at various sites. Their results have differed, depending on the site studied.

In 1991, Lotfi and Grunwald⁹ investigated the effects of caffeine on ocular blood flow. Oral administration of 200 mg caffeine caused a significant increase in blood pressure and a significant decrease in pulse rate. This was accompanied by a 13% decrease in macular blood flow at 1 hour after administration, compared to baseline. However, in that study, macular blood flow was measured by subjective quantification using a blue field entoptoscope. Furthermore, measurements were done at only two time points, before and 1 hour after caffeine administration. One reason our present study is significant is that the effects of caffeine on ocular fundus microcirculation (including the ONH) were objectively and sequentially determined.

We used a laser speckle method to evaluate the effects of caffeine on human ocular microcirculation. This method has recently been developed as a noninvasive means of measuring the microcirculation. Good reproducibility of measurements of ONH microcirculation in the human eye using the laser speckle method has been reported.¹³ In addition, a study using rabbits showed a correlation between changes in NB values of the ONH and changes in tissue blood flow.¹¹ Thus, the NB serves as an indicator of not only blood flow velocity but also tissue blood flow. Accordingly, use of the laser speckle method was considered appropriate for this study.

The 100-mg dose of caffeine administered in our study roughly corresponds to the amount of caffeine present in one cup of many popular beverages. Evaluation using larger doses of caffeine is of course necessary. However, greater changes in hemodynamic parameters induced by larger doses of caffeine might have had secondary effects on our results. We therefore decided to evaluate the effects of a relatively small amount of caffeine in this study.

Oral administration of 100 mg of caffeine significantly decreased the AUCs of SBR values in both the ONH and choroid-retina. This finding indicates that 100 mg of caffeine decreases microcirculation in the ONH and choroid-retina. The mean SBR values

Table 1. Changes in various parameters after administration of caffeine or placebo*

Parameters [†]	Baseline	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
100 mg caffeine									
MBP (mm Hg)	79.0 ± 2.0	79.4 ± 2.4	80.7 ± 1.9	79.6 ± 1.9	80.0 ± 1.0	78.0 ± 2.0	80.3 ± 2.1	80.0 ± 2.4	80.8 ± 2.3
PR (beats/min)	71.6 ± 4.3	69.5 ± 3.5	70.2 ± 3.7	69.5 ± 3.4	69.2 ± 3.7	69.7 ± 3.6	69.8 ± 3.5	69.0 ± 3.3	69.2 ± 3.4
IOP (mm Hg)	13.5 ± 0.9	13.7 ± 1.0	13.3 ± 0.9	13.0 ± 0.9	13.0 ± 0.9	13.0 ± 1.0	13.0 ± 1.1	13.1 ± 1.1	13.4 ± 1.0
OPP (mm Hg)	39.2 ± 1.4	39.3 ± 1.6	40.6 ± 1.1	40.1 ± 1.1	40.3 ± 0.8	39.0 ± 1.2	40.6 ± 1.8	40.2 ± 1.1	40.5 ± 1.7
Central CFF	40.8 ± 1.7	–	48.1 ± 1.7	–	47.6 ± 1.6	–	47.8 ± 1.6	–	47.6 ± 1.6
Placebo									
MBP (mm Hg)	78.0 ± 2.5	79.6 ± 2.5	80.8 ± 2.4	80.2 ± 2.9	79.1 ± 2.5	80.2 ± 2.7	80.6 ± 2.8	81.1 ± 3.4	80.3 ± 2.8
PR (beats/min)	74.0 ± 3.9	71.1 ± 3.1	71.2 ± 3.9	72.3 ± 3.1	70.9 ± 2.4	69.7 ± 3.5	72.0 ± 2.8	68.5 ± 3.1	70.5 ± 3.2
IOP (mm Hg)	13.9 ± 1.0	13.5 ± 1.1	13.5 ± 1.0	13.3 ± 1.1	13.4 ± 1.0	13.6 ± 1.0	13.7 ± 1.0	13.6 ± 1.0	13.2 ± 0.9
OPP (mm Hg)	38.1 ± 2.1	39.6 ± 1.8	40.3 ± 1.5	40.2 ± 1.9	39.4 ± 1.9	41.1 ± 2.0	40.0 ± 1.6	40.5 ± 2.0	40.3 ± 1.8
Central CFF	48.9 ± 1.3	–	49.1 ± 1.4	–	49.1 ± 1.4	–	49.2 ± 1.3	–	48.7 ± 1.4

*Values are mean ± SEM, n = 10.

[†]For all parameters, there were no significant differences in data between caffeine and placebo. MBP: mean blood pressure, PR: pulse rate, IOP: intraocular pressure, OPP: ocular perfusion pressure, CFF: critical fusion frequency.

reached a minimum from 45 to 60 minutes after caffeine administration in the ONH and from 45 to 75 minutes after administration in the choroid-retina. Our findings are in general agreement with data from previous studies^{21,22,35} of serial changes in plasma caffeine concentration (ie, peak values at 30 to 90 minutes). These results suggest that the decreased circulation in the ocular fundus caused by caffeine is dependent on its plasma concentration.

In the present study, there was a mean decrease of 6% in the choroid-retina at 60 minutes after oral administration of 100 mg caffeine. Lotfi and Grunwald⁹ reported a mean decrease of 13% at 60 minutes after oral administration of 200 mg caffeine. A direct comparison cannot be made between the two studies, because of differences in measurement sites and methods. However, the data does suggest that increased caffeine ingestion is associated with a further reduction in blood flow.

Shi et al³⁶ described considerable differences in caffeine absorption among individuals. Blanchard and Sawers²⁶ reported individual differences in caffeine elimination from the body, with half-lives of plasma concentration ranging from 2.7 to 9.9 hours. Grant et al³⁷ reported differences between Asian and Western subjects, with respect to the enzyme activity involved in caffeine metabolism. These findings indicate substantial individual differences in caffeine pharmacokinetics. In our study, the SBR values in the ONH and choroid-retina tended to decrease at all measurement time points after caffeine administration. However, the difference was only statistically significant for the 60-minute value in the ONH (Figure 1). As shown in Figure 2, however, the times at which SBRs reached their lowest values varied.

The individual differences were especially prominent in the choroid-retina. The individual differences in serial changes in blood flow caused by caffeine were offset when the mean values were calculated. This explains the apparent absence of significant changes at measurement time points other than 60 minutes in the ONH. However, comparison of AUCs (a parameter not affected by onset time of effect) did show significant differences. Therefore, although there are individual differences in onset times of caffeine effects on the ocular circulation, caffeine does indeed reduce blood flow in both the ONH and choroid-retina. In the present study, evaluation taking into account possible factors for differences in onset times of caffeine effects such as sex, age, body weight, and habits (eg, frequency and daily intake of caffeine) revealed no obvious trends. These differences may be explained by individual variations in rate of absorption and sensitivity to caffeine.

In our study, there were no significant changes in blood pressure, pulse rate, or central CFF. The medical literature describes changes in blood pressure and heart rate associated with ingestion of approximately 200 mg of caffeine. Prevention of deterioration of work performance has also been reported. However, we used 100 mg of caffeine in the present study, because this amount would likely have few systemic effects. In addition, there were no significant changes in IOP. After reviewing the literature concerning the effects of larger amounts of caffeine on IOP, we were even more certain that this smaller dose would have no obvious effects on IOP. Although some effect of caffeine on IOP cannot be completely excluded, this is probably small compared to its effects on tissue blood flow.

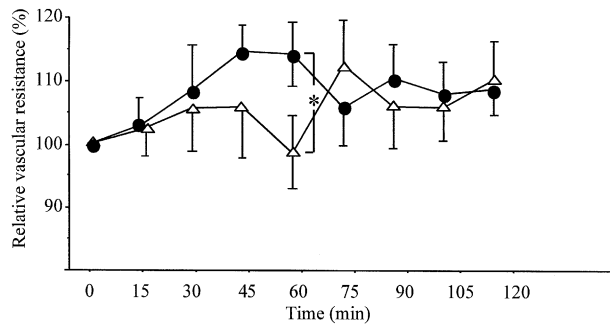


Figure 4. Sequential changes in relative optic nerve head vascular resistance. Relative vascular resistance is calculated as ratio of value obtained prior to administration. ●: Caffeine, △: control. n = 10, mean ± SE. *P < .05 (paired t-test with Bonferroni's correction).

ONH blood flow (BF), OPP, and ONH vascular resistance (R) are related by the following formula³⁸:

$$BF = OPP/R$$

Therefore, the relative R (R') is calculated as follows:

$$R' = OPP/SBR \text{ value in the ONH}$$

Figure 4 shows the sequential changes in R'. There was a significant increase in R' at 60 minutes, compared with administration of the control. This finding suggests that the observed decrease in ONH blood flow was due to an increase in peripheral vascular resistance. The fact that a small amount of caffeine, which induced no systemic effects, still reduced ocular fundus microcirculation suggests that caffeine may have a direct effect on ocular blood vessels.

This paper was originally published in Japanese in the *Nippon Ganka Gakkai Zasshi (J Jpn Ophthalmol Soc)* 2001;105:308–13. It appears here in a modified form after peer review and editing for the *Japanese Journal of Ophthalmology*.

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