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Can Psychologic Stress Elevate Intraocular Pressure in Healthy Individuals?

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Purpose: To investigate if a stress event can influence intraocular pressure (IOP) in a group of healthy individuals.

Design: Case-control study.

Participants: A total of 28 healthy subjects were included: 17 in the stress group and 11 in the control group.

Methods: The Trier Social Stress Test (TSST) is a tool to evaluate cortisol response to psychologic stimulation based on the stress induced by public speaking. All participants underwent a modified diurnal tension curve (DTC) 1 week before the TSST, with 3 IOP measurements performed between 8:00 AM and 2:00 PM. We evaluated the response to the TSST measuring the levels of salivary cortisol, IOP, and heart rate before, immediately after, and 40 minutes after TSST. The State Trait Anxiety Inventory (STAI) was applied to evaluate the levels of anxiety at the same time intervals.

Main Outcome Measures: Changes in IOP (mmHg), salivary cortisol, heart rate, and STAI scores.

Results: At baseline, there were no significant differences between case and controls regarding age (52.2 ± 6.26 vs. 53.8 ± 8.4 years, $P = 0.661$), gender (52.94% male vs. 45.45% female, $P = 0.669$), and ethnicity. Salivary cortisol (6.8 nmol/l, $P < 0.001$) and heart rate (7.2 beats/min, $P = 0.035$) increased significantly after the TSST. We observed a mean IOP increase of 1.0 mmHg (right eye, $P = 0.003$) and 1.1 mmHg (left eye, $P = 0.004$) when comparing IOP measurements obtained during the DTC and immediately after TSST. In addition, 35% (6/17) of the subjects in the TSST group showed an IOP increase higher than 2 mmHg after the test compared with 18% (2/11) in the control group. The STAI state score significantly increased after the stress event compared with baseline ($P = 0.026$) and decreased from poststress to the recovery period ($P = 0.006$) in the TSST group. The control group did not show significant changes in IOP, heart rate, salivary cortisol levels, and STAI scores.

Conclusions: Significant elevations of IOP, salivary cortisol, STAI scores, and heart rate occurred after inducing psychologic stress with TSST in a group of healthy individuals. *Ophthalmology Glaucoma 2020;3:426-433 © 2020 by the American Academy of Ophthalmology*

Stress is a complex biological response that prepares our body to deal with a variety of threats, both acute and chronic, protecting and restoring us to a steady state once the threat is gone.[1,2] Stress activates 2 main physiologic responses: the hypothalamopituitary adrenal pathway, which results in the release of cortisol, and the sympatho-adrenal medullary pathway, which leads to the release of adrenaline and noradrenaline.[3] However, the physiologic systems activated by stress not only can protect but also can be harmful.[4]

There is a consensus that both acute and chronic stress environments can lead to dysregulation of both systems (hypothalamopituitary adrenal and sympatho-adrenal medullary) in susceptible individuals, increasing the risk for the development of a variety of disorders, such as depression, anxiety, and cardiovascular diseases (systemic hypertension, atherosclerosis, and dyslipidemia).[5,6] Of note, data are scarce about the relationship between psychophysiologic stress and intraocular pressure (IOP) behavior. The majority of the available data suggest that IOP can be related to anxiety.[7-9]

Sauerborn et al[10] investigated the IOP response to a set of mental arithmetic tasks to induce psychologic stress in a group of myopes. They observed increased IOP measurements after the stress event, which was significantly higher in myopes compared with controls.[10] Later, Kaluza and Maurer[11] used the same mental stressor in a group of patients with glaucoma and found a significant increase in IOP immediately after exposition to the stress event.

Glaucoma is the leading cause of irreversible blindness and is expected to affect 111.8 million people worldwide in 2040.[12] Controlling and monitoring IOP is the only way to halt the development or the progression of the disease.[13] Several reports have shown an association between primary open-angle glaucoma with anxiety and depressive disorders.[14,15] Although we cannot establish causality between glaucoma and anxiety/depression disorders, investigating the relationship between IOP and psychophysiologic stress is important. If IOP increases after a stress event, we could promote antistress strategies in these individuals, reducing the risk for development or progression of glaucomatous damage.

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The purpose of this study is to evaluate the IOP behavior after applying a standardized protocol to induce psychologic stress in a group of healthy individuals.

Methods

Participants

This is a prospective, case-control study. We recruited participants from the Glaucoma Clinic at the Hospital Oftalmológico de Brasília. The Institutional Review Board at the Hospital Oftalmológico de Brasília approved the methods, and we obtained written informed consent from all participants. All study methods complied with the Declaration of Helsinki guidelines for human subject research. All subjects underwent a comprehensive ophthalmologic examination, including review of medical history (comorbidities, cigarette smoking, and alcohol consumption), visual acuity, slit-lamp biomicroscopy, IOP measurement (Goldmann applanation tonometry), gonioscopy with Posner goniolens, and dilated fundoscopic examination. We also performed in all subjects a modified diurnal tension curve (DTC) with 3 IOP measurements between 8:00 AM and 2:00 PM 1 week before the stress test. The DTC was performed to avoid regression to the mean effect.[16]

Groups

Inclusion criteria:

1. Subjects older than 18 years of age
2. Peak IOP <21 mmHg in the modified DTC
3. Open angle at gonioscopy
4. Optic disc with cup-to-disc ratio <0.6 with no signs of glaucomatous neuropathy

Exclusion criteria:

1. Presence of any ocular disease (with the exception of refractive errors)
2. Anxiety or depressive disorders
3. Use of medication for anxiety or depressive disorders
4. History of ocular trauma or surgery
5. Pregnancy
6. Use of any kind of oral/topical steroids
7. Cushing syndrome
8. Congenital adrenal hyperplasia
9. Adrenal insufficiency

Both age and sex can affect the response to stress. For instance, older adults seem to have lower cortisol responses to the Trier Social Stress Test (TSST).[17] Furthermore, men seem to have higher baseline salivary cortisol than women and are more likely to have increased cortisol in response to the stress event.[18] Therefore, we performed pair matching, with a ratio of 2:1, in which clusters were paired on the basis of their potential confounders (age and sex) and then, within each pair, 1 cluster was randomized to TSST or the control group.

Trier Social Stress Test

The TSST was developed in 1993 to evaluate psychologic stress induced by public speaking.[19] It incorporates social evaluation and unpredictability by obliging the person to speak in front of an unresponsive audience and completing a surprise mental arithmetic test. The TSST can elevate cortisol levels 2- to 3-fold compared with nonstress control conditions.[20,21] The TSST procedure is widely used in stress laboratories worldwide and is currently considered the gold standard in human experimental stress research.[20] We followed the protocol described next, as described in a previous article.[22]

Setting Up

We used 5 distinct areas to perform the TSST protocol: 1 waiting room for the control group, 1 waiting room for the case participants before beginning the TSST, 1 room for recovery periods, a room for speech preparation before the interview, and an interview room to evaluate speech performance and the arithmetic task. The interview room was arranged so that the participant faced the interviewers. Video and audio recording equipment were in the visual field of the participant. All interviewers wore a laboratory coat during the TSST to increase stress during the test. We instructed interviewers to maintain eye contact with the participants and to refrain from making emotional facial expressions.

Salivary Cortisol

All subjects were submitted to a 3-hour fasting period for food and beverage (other than water) before salivary cortisol measurements. Also, patients were not allowed to smoke before the beginning of the TSST protocol. The *Salivette* system (Sarstedt, Numbrecht, Germany) was used to collect a sample of saliva. The system is placed in the mouth, chewed for approximately 1 minute, and then transferred into the tube. The swab can hold between 0.5 and 3 ml of saliva. Salivary cortisol was measured by an immunoassay method.[23] The salivary cortisol is generally used to assess pituitary-adrenal function in patients with Cushing disease, with sensitivity higher than 80% and 92.3% specificity.[24] For healthy subjects, morning levels of cortisol in saliva below 20.30 nmol/l are considered within the normal range.[25]

State Trait Anxiety Inventory

The State Trait Anxiety Inventory (STAI) was developed by Gaudry et al[26] in 1970 and has been used without significant modifications to assess psychologic stress. This questionnaire contains 40 statements (divided equally in 2 parts) about the feelings of the participant. In the first part, subjects are instructed to indicate the intensity of their feelings of anxiety at a particular moment (state anxiety), using scores ranging from 1 (absolutely not) to 4 (very much). In the second part, subjects describe how they generally feel (trait anxiety) by reporting the frequency of their symptoms of anxiety, again using scores ranging from 1 (hardly ever) to 4 (often).[27] The total score of each part may range between 20 and 80, with higher scores indicating higher levels of anxiety. This instrument was previously validated into Brazilian Portuguese by Biaggio and Natalício.[28]

Prestress Measurements

After the patients remained in the waiting room for 45 minutes, we measured the IOP with the Goldmann applanation tonometer and the heart rate with a finger pulse oximeter (G-Tech, Beijing Choice Electronic Technology, Beijing, China). The STAI was then applied to assess prestress anxiety. Subsequently, we performed the collection of a prestress salivary cortisol. We instructed patients to chew the *Salivette* system. All samples were labeled and stored at −20°C. We then brought the participant to the speech preparation room, where the following script was read to the participant: "This is the speech preparation portion of the task; you need to prepare a 5-minute speech describing why you would be a good candidate for a job at Hospital Oftalmológico de Brasília. Your speech will be videotaped and reviewed by a panel of judges trained in public speaking. You have 10 minutes to prepare, and your time begins now."

Speech and Math Tasks

After 10 minutes, we took the subjects from the speech preparation area to the interview room and read the following script to the participant: "This is the speech portion of the task. You are to deliver a speech describing why you would be a good candidate for this job. You should speak for the entire 5-minute time period. Your time begins now." We turned on the video camera, and the participant began the speech. If the participant stopped talking during the speech, we allowed him (or her) to remain silent for 20 seconds. If the subject did not resume speaking, we instructed him (or her) by saying: "You still have time remaining."

At the end of the 5-minute speech, the following script was read to the participant: "During the final 5-minute math portion of this task, you will be asked to sequentially subtract the number 13 from 1022. You will verbally report your answers aloud and be asked to start over from 1022 if a mistake is made. Your time begins now." If the participant made a mistake, we would tell him (or her): "That is incorrect, please start over from 1022." During this task, we used a digital timer to control the 5-minute limit and measured the heart rate once. At the end of the math performance period of the TSST, we measured the IOP, the heart rate, collected a "stress" saliva sample (within a 10-minute timeframe), and administered the poststress STAI.

Recovery Measurements

We took participants to the recovery room, where they waited for 40 minutes. We used this time to explain to the participant the true nature of the experiment, clarifying that their performance was not recorded and that no analysis of their speech or math performance would be conducted. We then measured the recovery IOP and heart rate, and collected new saliva sample; subjects were instructed to complete the recovery STAI.

All the interviews, IOP, and cortisol measurements were made between 8:00 AM and 2:00 PM to allow a comparison with the modified DTC made 1 week before the TSST. The control group did not perform the TSST, but underwent the same IOP, salivary cortisol, heart rate, and STAI measurements, respecting the same time intervals of the TSST group. One investigator (TCS) performed all IOP measurements, and another investigator (ID) performed all salivary cortisol measurements. Both of them were masked to the identity of the patients.

Statistical Analysis

Normality of the variables was assessed using the Skewness-Kurtosis test. Descriptive statistics included mean and standard deviation and Student t tests for normally distributed (using 1-tailed test) and median, interquartile range, and Wilcoxon rank-sum for nonparametrically distributed variables. For categoric variables, we used the Fisher exact test. We evaluated magnitude of change for different time points (baseline, stress, poststress, and recovery) for variables such as IOP, salivary cortisol, heart rate, and STAI scores. All statistical analyses were conducted with STATA version 13 (StataCorp LP, College Station, TX). The alpha level (type I error) was set at 0.05.

Results

We included a total of 28 healthy individuals in the study: 17 in the TSST group and 11 as controls. No difference was found between groups regarding age, sex, ethnicity, systemic medication, comorbidities, alcohol consumption, and smoking habit (Table 1).

Table 1. Baseline Clinical and Demographic Variables of Subjects Included in the Study

Variables	Case (17 Subjects)	Control (11 Subjects)	P Value
Age, yrs	52.2 ± 6.26	53.8 ± 8.41	0.661
Gender, % female	52.94%	45.45%	0.699
Race			
% White	52.94%	45.45%	0.378
% African American	35.29%	54.55	
% Asian	11.76%	0%	
Systemic hypertension, yes	23.53%	18.18%	0.736
Diabetes, yes	11.76%	9.09%	0.823
Cigarette smoking, yes	11.76%	9.09%	0.823
Alcohol consumption, yes	29.41%	36.35%	0.700

We observed that salivary cortisol levels were significantly higher in cases than in controls both after the TSST (11.8 ± 5.91 vs. 3.5 ± 1.81 nmol/l, $P < 0.001$) and in the recovery period (5.3 ± 2.42 vs. 3.4 ± 2.11 nmol/l, $P = 0.020$) (Table 2). No statistically significant differences in IOP and heart rate measurements were observed when comparing cases with controls. The STAI state score after the TSST was significantly higher in cases (41.8 ± 7.48) than in controls (34.2 ± 7.65, $P = 0.007$) (Table 2).

When we evaluated the IOP change from DTC measurements among participants of the TSST group, we observed significant IOP increases in both the right eye (1.0 ± 1.41 mmHg, $P = 0.003$) and the left eye (1.1 ± 1.57 mmHg, $P = 0.004$) (Table 3). In addition, when we compared IOP measurements immediately before and after TSST, we observed significant mean IOP elevations of 0.7 ± 1.40 mmHg ($P = 0.027$) and 0.5 ± 1.32 mmHg ($P = 0.047$) in the right and left eye, respectively. During the recovery period, the mean IOP declined significantly at approximately 0.8 mmHg in both eyes ($P = 0.004$) (Table 3). No significant IOP change was observed in the control group. We found that 35% (6/17) of subjects in the TSST group showed an IOP increase higher than 2 mmHg, comparing the mean IOP obtained during the DTC and the mean IOP after the stress event, whereas only 18% (2/11) in the control group had the same change ($P = 0.419$).

The salivary cortisol increased significantly after patients underwent the TSST (6.8 ± 5.65 nmol/l, $P < 0.001$). We also observed an increase in the heart rate of patients after the TSST (7.2 ± 13.90 beats/min, $P = 0.035$), although the magnitude of change was more dramatic when comparing interview and recovery measurements (a decrease of 11.7 ± 16.82 beats/min, $P = 0.010$) (Table 3). Again, no change was observed in the cortisol level and heart rate in the control group.

In Table 4, we list the STAI scores in subjects performing the TSST. The STAI state score significantly increased after the stress event compared with baseline ($P = 0.026$) and decreased from poststress to the recovery period ($P = 0.006$). No change was observed in the STAI trait scores when baseline and poststress scores were compared, but both groups showed a significant decrease (2.1 ± 4.20, 2.81 ± 3.15; $P = 0.024$, $P = 0.014$; case and control, respectively) after recovery (Table 4).

Table 2. Salivary Cortisol, Intraocular Pressure, Heart Rate, and State Trait Anxiety Inventory Scores of Subjects Included in the Study

Variables	Case (17 Subjects)	Control (11 Subjects)	*P* Value
Salivary cortisol, nmol/l			
Baseline	4.9 ± 2.56	3.9 ± 2.08	0.248
Stress	11.8 ± 5.91	3.5 ± 1.81	<0.001
Recovery	5.3 ± 2.42	3.4 ± 2.11	0.020
IOP right eye, mmHg			
DTC	13.0 ± 2.23	14.2 ± 1.73	0.121
Baseline	13.3 ± 2.89	13.5 ± 0.70	0.854
Stress	14.0 ± 2.65	14.2 ± 2.76	0.839
Recovery	13.2 ± 2.43	13.8 ± 2.13	0.523
IOP left eye, mmHg			
DTC	13.1 ± 2.23	14.4 ± 1.59	0.105
Baseline	13.6 ± 2.59	14.0 ± 0.74	0.727
Stress	14.2 ± 2.86	14.3 ± 2.69	0.906
Recovery	13.3 ± 2.44	13.9 ± 2.42	0.560
Heart rate, beats/min			
Prestress	71.5 ± 13.18	71.5 ± 11.17	0.990
Interview	78.7 ± 13.06	N/A	N/A
Poststress	73.6 ± 17.57	69.7 ± 9.69	0.295
Recovery	67.0 ± 13.78	68.7 ± 10.49	0.784
STAI trait (score range, 20–80)			
Baseline	43.7 ± 10.83	40.3 ± 9.35	0.409
Poststress	43.4 ± 10.66	40.0 ± 11.08	0.422
Recovery	41.2 ± 8.89	37.1 ± 10.40	0.280
STAI state (score range, 20–80)			
Baseline	37.8 ± 8.76	36.9 ± 7.59	0.779
Poststress	41.8 ± 7.48	34.2 ± 7.65	0.007
Recovery	39.2 ± 8.96	35.2 ± 9.89	0.275

DTC = diurnal tension curve; IOP = intraocular pressure; N/A = not applicable; STAI = State Trait Anxiety Inventory.

Discussion

The current study demonstrated that a standardized stress event increased IOP in a group of healthy individuals. Intraocular pressure is the most common risk factor for the development of glaucoma and the only modifiable risk factor to prevent the development or progression of glaucoma.[13,29] Because glaucoma and anxiety disorders frequently coexist, it is important to better understand the relationship between psychologic stress and IOP.[30,31]

Table 3. Intraocular Pressure, Salivary Cortisol, and Heart Rate Changes during the Study

IOP Magnitude of Change, mmHg	Mean DTC vs. IOP Stress	*P* Value	Basal IOP vs. IOP Stress	*P* Value	IOP Stress vs. IOP recovery	*P* Value
Case (right eye)	1.0 ± 1.41	0.003	0.7 ± 1.40	0.027	0.8 ± 1.13	0.004
Control (right eye)	0.0 ± 2.15	0.500	0.0 ± 1.34	0.103	0.4 ± 1.21	0.242
Case (left eye)	1.1 ± 1.57	0.004	0.5 ± 1.32	0.043	0.8 ± 1.21	0.004
Control (left eye)	0.0 ± 2.25	0.930	0.0 ± 1.20	0.340	0.4 ± 1.12	0.211

Salivary Cortisol Magnitude of Change, nmol/l	Basal Cortisol vs. Cortisol Stress	*P* value	Cortisol Stress vs. Cortisol recovery	*P* value
Case	6.8 ± 5.65	<0.001	6.5 ± 5.56	<0.001
Control	0.3 ± 1.88	0.575	0.1 ± 1.84	0.781

Heart Rate Magnitude of Change, beats/min	Prestress vs. Interview	*P* Value	Interview vs. Poststress	*P* Value	Interview vs. Recovery	*P* Value
Case	7.2 ± 13.90	0.035	5.1 ± 17.83	0.151	11.7 ± 16.82	0.010

Heart Rate Magnitude of Change, beats/min	Prestress vs. Poststress	*P* Value	Poststress vs. Recovery	*P* Value
Control	1.8 ± 6.06	0.448	1.0 ± 10.29	0.805

DTC = diurnal tension curve; IOP = intraocular pressure.

Table 4. State Trait Anxiety Inventory Changes during the Study

STAI State Magnitude of Change	Prestress vs. Poststress	P Value	Poststress vs. Recovery	P Value
Case	4.0 ± 7.88	0.026	2.5 ± 3.69	0.006
Control	2.6 ± 5.59	0.148	1.0 ± 7.60	0.617
STAI Trait Magnitude of Change	**Prestress vs. Poststress**	**P Value**	**Poststress vs. Recovery**	**P Value**
Case	0.2 ± 3.51	0.367	2.1 ± 4.20	0.024
Control	0.3 ± 5.39	0.827	2.81 ± 3.15	0.014

STAI = State Trait Anxiety Inventory.

We found that among the group submitted to the TSST, a mean of 1.0 and 1.1 mmHg (right and left eyes, respectively) increase in IOP were observed when mean DTC measurements were compared with post-TSST measurements. Although it achieved statistical significance in both eyes ($P = 0.003$ and $P = 0.004$, respectively), one may wonder whether this IOP increase is clinically meaningful. It is important to highlight that 35% (6/17) of subjects in the TSST group showed an IOP increase higher than 2 mmHg, whereas only 18% of eyes in the control group had similar IOP elevations. Although the current study evaluated a short-term IOP increase, several population-based studies have described chronic high levels of IOP as a risk factor for glaucoma.[32-34] The Barbados Eye Study, which included 3222 subjects older than 40 years of age, revealed that baseline IOP was a significant risk factor for development of glaucoma during a follow-up of 9 years.[35] For every 1 mmHg increase in baseline IOP, there was a 12% increased risk of incidence of glaucoma (confidence interval from risk ratio 1.08−1.16). In the Visual Impairment Project, which included 3271 Australian individuals older than 40 years of age, each 1-mmHg increase in baseline IOP was associated with a 10% increase (confidence interval from risk ratio 1.04−1.12) in the risk of developing of glaucoma.[36] Thus, the literature has evidence suggesting that even modest elevations of IOP can increase the risk for the development of glaucoma.

In the current study, we evaluate the effect of an acute stressor event. The IOP elevation may be caused by an autonomic nervous system response to stress.[37] Although the exact mechanisms that control the rhythm of aqueous humor production are poorly understood, the lack of balance on adrenergic stimulation could modify the aqueous humor production rate and decrease outflow facility.[38] In addition, chronic endogenous elevation of cortisol levels secondary to psychologic stress could eventually cause permanent damage to the trabecular meshwork.[39] Every system of the human body can respond to acute events, releasing mediators that promote adaptation and survival. However, when these acute stressors are overused or inefficiently managed, an overload of the system may occur.[40]

Previous studies have already used acute stressors to evaluate the behavior of cardiovascular physiology and the ocular response to stress.[41] The TSST is based on the stress induced by public speaking, and hundreds of research studies have used the TSST to examine the impact of acute stress on human neurobiology.[20] Woo et al[42] performed a study with 20 normal individuals to assess the effects of psychosocial stress (induced by TSST) on the IOP and lacrimal secretion. The mean IOPs before and after TSST were 14.52 ± 3.18 mmHg and 15.08 ± 3.18 mmHg, respectively ($P = 0.240$). Although this change was not statistically significant, the authors found that the mean post-TSST IOP (15.08 ± 3.18 mmHg) was significantly higher than the mean IOP measured 1 week after performing the TSST (14.18 ± 3.30 mmHg, $P = 0.027$). In our study, significant IOP increases were observed when poststress measurements were compared with both the IOP measured immediately before the TSST and the mean IOP measured during a modified DTC obtained 1 week before the TSST (Table 2).

Jimenez and Vera[43] investigated the effect of an acute stress (academic examination) on the IOP of 33 healthy University students. A repeated-measures design was used with 2 different conditions (examination and control). A Bayesian statistical analysis showed significantly higher IOP values in the examination session in comparison with the control condition ($P < 0.001$). Brody et al[44] studied the effects of psychologic stress (5-minute mental arithmetic tasks) on the IOP of 49 healthy adults and reported a statistically significant elevation of 1.3 mmHg ($P < 0.001$) after the stressor. However, none of the previous studies had a control group that was not submitted to a stress test. The absence of significant IOP, heart rate, and cortisol level changes in this group suggests that IOP, cortisol, and heart rate elevations in healthy individuals submitted to the TSST were real (Table 3).

It is important to investigate if the basal anxiety level could influence the IOP response to a stress event. Mendez-Ulrich et al[7] investigated the effect of "white coat ocular hypertension" in 61 healthy subjects to evaluate whether an anticipatory anxiety state or trait could predict an IOP elevation in an artificial clinical setting. They found that IOP at arrival to the simulated clinical setting was 2.62 and 1.93 mmHg higher (for the right and left eyes, respectively) in participants who had a high anxiety state in comparison with those who had a low anxiety state. Although we used different questionnaires to assess anxiety levels, we also observed a significant increase in the STAI state score (mean of 4.0, $P = 0.026$) in subjects undergoing the TSST, whereas the STAI trait did not show a significant change.

The current study did not evaluate the stress response in patients with glaucoma. However, evidence suggests that

patients with glaucoma also might have an increase in IOP after stress events. Kaluza and Maurer[11] investigated the impact of a mental stressor test on the IOP of patients with open-angle glaucoma. They observed that immediately after exposition to the mental stressor, a mean IOP increase of 1.5 mmHg was noted, and after a 10-minute recovery period, the mean IOP returned to baseline levels. Recently, a case report from Gillmann et al[9] described a 78-year-old patient with pseudoexfoliative glaucoma who presented an acute asymmetrical increase in IOP immediately after an emotional stress.[9] In their investigation, no other cause for the transient acute hypertensive episode was found, and the authors suggested that the IOP peak might have been caused by the acute stressor event experienced by the patient. These studies highlight the importance of further investigation of the IOP response to acute or chronic stress.

Another way to assess the effects of stress on patients with glaucoma is to measure the IOP behavior following therapies designed to reduce stress. Recently, Dada et al[45] evaluated the effects of mindfulness-based stress reduction on IOP and stress biomarkers in a randomized trial including 90 patients with glaucoma. Patients were divided into a 21-day mindfulness meditation group or a control group. The results showed significant mean IOP reductions in meditators (right eye: from 18.8 to 12.7 mmHg and left eye: from 19.0 to 13.1 mmHg, $P < 0.001$), which correlated significantly with systemic cortisol levels (497.3 to 392.3 ng/ml, $P < 0.001$) and other stress biomarkers. Further research, with long-term, prospective, randomized trials, is needed to validate these antistress methods as useful therapies to reduce the risk for development or progression of glaucoma.

Study Limitations

The present study has several limitations. First, the modest magnitude of IOP change could be due to examiner variability or tonometry error.[46] However, we tried to minimize this effect by eliminating interobserver variability (the same investigator performed all IOP measurements) and by using the same calibrated Goldmann applanation tonometer in all patients to avoid device calibration error. Moreover, 35% (6/17) of subjects in the TSST group showed an IOP increase higher than 2 mmHg after the stressor, whereas only 18% in the control group had similar IOP elevations. Second, we did not include patients with glaucoma, and our results may not reflect the outcomes in older patients or those at risk for glaucoma, because the mean age was 50 years in both groups (Table 1). The compensatory mechanisms to stress and its ability to mitigate IOP increase may be compromised in older adults. Evidence suggests that older individuals have distinct patterns of diurnal cortisol and that reactivity to psychosocial challenges increase with age.[47,48] Our findings may be understated, because an older population (with higher risk for glaucoma) may have a larger increase in IOP due to age-related changes in their physiology and a lower ability to adjust to fluctuating stressors within ocular tissues.[49] We plan to continue recruiting patients to report the outcomes in older subjects and patients with glaucoma in the future. Third, the small sample size limited the possibility of performing a logistic regression to evaluate odds ratios of studied variables. Nevertheless, the increase in salivary cortisol and heart rate validated the effect of the TSST as an acute stressor tool. Finally, we could not evaluate the effect of chronic stress in this protocol. A prospective, longitudinal study identifying possible stressor events in a large group of patients could be useful to determine if chronic psychologic stress is a risk factor for glaucoma progression.

In conclusion, this study showed that a significant IOP elevation might occur after an acute psychologic stress event in healthy subjects. This finding is in agreement with previous studies. Although it is hard to establish causality between glaucoma and anxiety/depression disorders, our findings suggest that if stress is induced by these comorbidities, the resulting IOP increase may act as a risk factor for glaucoma development.

References

1. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med*. 1998;338:171–179.
2. Turner AI, Smyth N, Hall SJ, et al. Psychological stress reactivity and future health and disease outcomes: a systematic review of prospective evidence. *Psychoneuroendocrinology*. 2020;114:104599.
3. Chrousos GP. Stress and disorders of the stress system. *Nat Rev Endocrinol*. 2009;5:374–381.
4. Selye H. A syndrome produced by diverse nocuous agents. 1936. *J Neuropsychiatry Clin Neurosci*. 1998;10:230–231.
5. Mazure CM. Life stressors as risk factors in depression. *Clin Psychol Sci Pract*. 1998;5:291–313.
6. Vanitallie TB. Stress: a risk factor for serious illness. *Metabolism*. 2002;51(6 Suppl 1):40–45.
7. Mendez-Ulrich JL, Sanz A, Feliu-Soler A, et al. Could white coat ocular hypertension affect to the accuracy of the diagnosis of glaucoma? Relationships between anxiety and intraocular pressure in a simulated clinical setting. *Appl Psychophysiol Biofeedback*. 2018;43:49–56.
8. Shily BG. Psychophysiological stress, elevated intraocular pressure, and acute closed-angle glaucoma. *Am J Optom Physiol Opt*. 1987;64:866–870.
9. Gillmann K, Hoskens K, Mansouri K. Acute emotional stress as a trigger for intraocular pressure elevation in glaucoma. *BMC Ophthalmol*. 2019;19:69.
10. Sauerborn G, Schmitz M, Franzen U, Florin I. Stress and intraocular pressure in myopes. *Psychol Health*. 1992;6:61–68.
11. Kaluza G, Maurer H. Stress and intraocular pressure in open angle glaucoma. *Psychol Health*. 1997;12:667–675.
12. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014;121:2081–2090.
13. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA*. 2014;311:1901–1911.
14. Mabuchi F, Yoshimura K, Kashiwagi K, et al. High prevalence of anxiety and depression in patients with primary open-angle glaucoma. *J Glaucoma*. 2008;17:552–557.
15. Lin HC, Chien CW, Hu CC, Ho JD. Comparison of comorbid conditions between open-angle glaucoma patients and a

control cohort: a case-control study. *Ophthalmology*. 2010;117:2088–2095.
16. Bhorade AM, Gordon MO, Wilson B, et al. Ocular Hypertension Treatment Study Group. Variability of intraocular pressure measurements in observation participants in the ocular hypertension treatment study. *Ophthalmology*. 2009;116:717–724.
17. Hidalgo V, Pulopulos MM, Puig-Perez S, et al. Acute stress affects free recall and recognition of pictures differently depending on age and sex. *Behav Brain Res*. 2015;292:393–402.
18. Uhart M, Chong RY, Oswald L, et al. Gender differences in hypothalamic–pituitary–adrenal (HPA) axis reactivity. *Psychoneuroendocrinology*. 2006;31:642–652.
19. Kirschbaum C, Pirke KM, Hellhammer DH. The "Trier Social Stress Test"—a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology*. 1993;28:76–81.
20. Allen AP, Kennedy PJ, Dockray S, et al. The Trier social stress test: principles and practice. *Neurobiol Stress*. 2017;6:113–126.
21. Frisch JU, Häusser JA, Mojzisch A. The Trier Social Stress Test as a paradigm to study how people respond to threat in social interactions. *Front Psychol*. 2015;6:14.
22. Birkett MA. The Trier Social Stress Test protocol for inducing psychological stress. *J Vis Exp*. 2011;56:3238.
23. Dressendörfer RA, Kirschbaum C, Rohde W, et al. Synthesis of a cortisol-biotin conjugate and evaluation as a tracer in an immunoassay for salivary cortisol measurement. *J Steroid Biochem Mol Biol*. 1992;43:683–692.
24. Belaya ZE, Iljin AV, Melnichenko GA, et al. Diagnostic performance of late-night salivary cortisol measured by automated electrochemiluminescence immunoassay in obese and overweight patients referred to exclude Cushing's syndrome. *Endocrine*. 2012;41:494–500.
25. Trilck M, Flitsch J, Lüdecke DK, et al. Salivary cortisol measurement—a reliable method for the diagnosis of Cushing's syndrome. *Exp Clin Endocrinol Diabetes*. 2005;113:225–230.
26. Gaudry E, Vagg P, Spielberger CD. Validation of the State-Trait Distinction in anxiety research. *Multivariate Behav Res*. 1975;10:331–341.
27. Leal PC, Goes TC, da Silva LCF, Teixeira-Silva F. Trait vs. state anxiety in different threatening situations. *Trends Psychiatry Psychother*. 2017;39:147–157.
28. Biaggio A, Natalício L. *Manual para o inventário de ansiedade Traço-Estado (IDATE)*15. Rio de Janeiro: CEPA; 1979.
29. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol*. 2002;120:1268–1279.
30. Zhang X, Olson DJ, Le P, et al. The association between glaucoma, anxiety, and depression in a large population. *Am J Ophthalmol*. 2017;183:37–41.
31. Rezapour J, Nickels S, Schuster AK, et al. Prevalence of depression and anxiety among participants with glaucoma in a population-based cohort study: The Gutenberg Health Study. *BMC Ophthalmol*. 2018;18:157.
32. Leske MC, Connell AM, Schachat AP, Hyman L. The Barbados Eye Study. Prevalence of open angle glaucoma. *Arch Ophthalmol*. 1994;112:821–829.
33. Quigley HA, West SK, Rodriguez J, et al. The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. *Arch Ophthalmol*. 2001;119:1819–1826.
34. Coleman AL, Miglior S. Risk factors for glaucoma onset and progression. *Surv Ophthalmol*. 2008;53(Suppl 1):S3–S10.
35. Leske MC, Wu SY, Hennis A, et al. Risk factors for incident open-angle glaucoma: the Barbados Eye Studies. *Ophthalmology*. 2008;115:85–93.
36. Le A, Mukesh BN, McCarty CA, Taylor HR. Risk factors associated with the incidence of open-angle glaucoma: the visual impairment project. *Invest Ophthalmol Vis Sci*. 2003;44:3783–3789.
37. Hoyng PFJ. The autonomic nervous system and the intraocular pressure. In: *Pharmacological Denervation and Glaucoma. Monographs in Ophthalmology 2*. Dordrecht: Springer; 1981:; 2.
38. Goel M, Picciani RG, Lee RK, Bhattacharya SK. Aqueous humor dynamics: a review. *Open Ophthalmol J*. 2010;4:52–59.
39. Weinreb RN, Bloom E, Baxter JD, et al. Detection of glucocorticoid receptors in cultured human trabecular cells. *Invest Ophthalmol Vis Sci*. 1981;21:403–407.
40. Mcewen BS. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Ann N Y Acad Sci*. 2004;1032:1–7.
41. Herbison CE, Henley D, Marsh J, et al. Characterisation and novel analyses of acute stress response patterns in a population-based cohort of young adults: influence of gender, smoking and BMI. *Stress*. 2016:1–29.
42. Woo YJ, Kim JE, Rah SH, et al. The effects of stress on intraocular pressure and lacrimal secretion. *J Korean Ophthalmol Soc*. 2012;53(9):1304–1310.
43. Jimenez R, Vera J. Effect of examination stress on intraocular pressure in university students. *Appl Ergon*. 2018;67:252–258.
44. Brody S, Erb C, Veit R, Rau H. Intraocular pressure changes: the influence of psychological stress and the Valsalva maneuver. *Biol Psychol*. 1999;51:43–57.
45. Dada T, Mittal D, Mohanty K, et al. Mindfulness meditation reduces intraocular pressure, lowers stress biomarkers and modulates gene expression in glaucoma: a randomized controlled trial. *J Glaucoma*. 2018;27:1061–1067.
46. Whitacre MM, Stein R. Sources of error with use of Goldmann-type tonometers. *Surv Ophthalmol*. 1993;38:1–30.
47. Gaffey AE, Bergeman CS, Clark LA, Wirth MM. Aging and the HPA axis: stress and resilience in older adults. *Neurosci Biobehav Rev*. 2016;68:928–945.
48. Kudielka BM, Buske-Kirschbaum A, Hellhammer DH, Kirschbaum C. HPA axis responses to laboratory psychosocial stress in healthy elderly adults, younger adults, and children: impact of age and gender. *Psychoneuroendocrinology*. 2004;29:83–98.
49. Becker B. The decline in aqueous secretion and outflow facility with age. *Am J Ophthalmol*. 1958;46(5 Part 1):731–736.

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Author Contributions:

Conception and design: Abe, Silva, Costa

Data collection: Abe, Silva, Dantas, Curado, Madeira, de Souza

Analysis and interpretation: Abe, Costa

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Abbreviations and Acronyms:
DTC = diurnal tension curve; **IOP** = intraocular pressure; **STAI** = State Trait Anxiety Inventory; **TSST** = Trier Social Stress Test.

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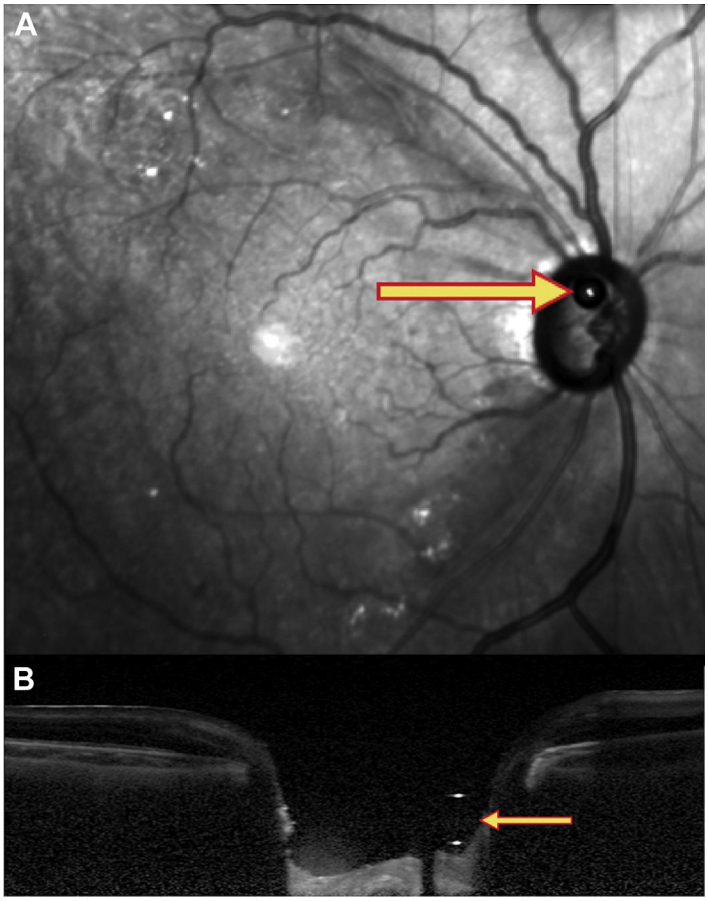
Pictures & Perspectives



Gas Bubble in a Glaucomatous Cup

A 56-year-old man with a known case of primary open-angle glaucoma underwent vitrectomy surgery for macular hole. At 1-month follow up, the macular hole was closed, and the retina was well attached. A small gas bubble was observed on the glaucomatous optic cup (Fig **A**). On spectral-domain (SD) OCT there was presence of a double reflectivity in the cup demonstrating the presence of the gas bubble (Fig **B**). Since he had a deep optic disc cup due to glaucoma, the bubble found a space to settle down on the optic disc giving a vivid appearance on SD OCT and infrared imaging. (Magnified version of Fig **A**-**B** is available online at www.ophthalmologyglaucoma.org/).

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