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Analysis of aerobic exercise influence on intraocular pressure and ocular perfusion pressure in patients with primary open-angle glaucoma: A randomized clinical trial

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Purpose: To investigate the change pattern of ocular perfusion pressure (OPP) and intra-ocular pressure (IOP) after short-term and long-term aerobic exercise. **Methods:** In this prospective, single-masked, randomized clinical trial, 123 patients with a primary open angle glaucoma that locally used prostaglandin analog alone were randomly divided into the exercise and control groups. In the short-term study, all individuals underwent a cycling exercise at moderate intensity (20% Wmax for 10 minutes) and high intensity (60% Wmax for 5 minutes). During the long-term study, the exercise group is characterized by regular jogging exercise lasting for 30 minutes during 6: 00–10: 00 in the morning for 3 months, with the exercise frequency of at least 20 times per month, and with the intensity reflected by the target heart rate. The control group is designed as a group with irregular exercise. **Results:** After short-term aerobic exercise, IOP significantly decreased, whereas the ocular perfusion pressure (OPP) significantly increased. The decreasing amplitude of IOP is related to the baseline of IOP, the intensity of exercise, gender, and so on. After 3 months of long-term exercise, the changes in the IOP level of the exercise group indicated a decreasing trend. **Conclusion:** The significant decrement of IOP and the increment of OPP suggest that aerobic exercise is beneficial for patients with primary open-angle glaucoma and appropriate aerobic exercise is appropriate in treating glaucoma patients.

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Glaucoma is currently the most common irreversible cause of blindness. Primary open-angle glaucoma (POAG) is the predominant sub-type, accounting for 74% of all glaucoma cases.[1] POAG is a chronic, progressive, potentially blinding, irreversible eye disease causing optic nerve rim and retinal nerve fiber layer (RNFL) loss with related visual field (VF) defects. Angle appearance is normal, and major risk factors include the level of intra-ocular pressure (IOP) and older age.[2] The adult population (40–80 years old) cases were estimated to reach 79.76 in 2040.[3,4] The progression of glaucoma is closely related to the IOP level, which remains an undeniable risk factor.[5-8] According to the results of the Early Manifest Glaucoma Trial (EMGT), the risk of glaucomatous progression lowers by 10% for every 1 mmHg reduction.[9] The management of POAG has focused on reducing IOP.[10,11] The current treatments for all POAG patients comprise incisional surgery, laser surgery, and medication. However, monotherapy might be impotent to produce the required drop in IOP for some patients, or some of the approaches have problems of high costs and clinical side effects. In some cases, monotherapy is only partially efficacious. Adjuvant therapy and other treatments with different mechanisms can be added to form combination therapy.[12] Reducing IOP by exercise as an adjuvant therapy has become prevalent in the field of glaucoma because of its low expenditure and convenience. It is easier for patients' self-management.

The method of decreasing IOP with dynamic exercise was established by Janiszewska-Zygier[13] in 1963. There was a significant IOP decrease after dynamic exercise.[14-16] Walking, jogging, and cycling are joint aerobic exercises that cause slight but significant IOP reduction with 15–20 minutes of endurance while simultaneously elevating the heart rate.[17-19] The results show that[20] patients on pharmacological glaucoma therapy could still obtain a 5.72 ± 3.34 mmHg IOP decrease after exercise. Karabatakis *et al*.[21] reported that the post-exercise IOP decrease in ordinary people was 1 to 8 mmHg, whereas Qureshi[22] reported that glaucoma patients could have a 7.72 ± 2.05 mmHg post-exercise IOP decrease.

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Although significant IOP decreases were widely reported in previous essays, whether the ocular perfusion pressure (OPP) increases or decreases is still controversial. The ocular blood flow, which highly correlated to the IOP level, consists of retinal and choroidal circulation. The OPP, the net pressure gradient representing blood flow to the eye, refers to the relationship between systemic blood pressure (BP) and IOP. The OPP is calculated as 2/3 mean arterial pressure (MAP)–IOP, where MAP = diastolic BP + 1/3 (systemic BP–diastolic BP).[23] Both dynamic and isometric exercises can elevate the OPP, which suggests a beneficial effect on patients with glaucoma as the subjects with low OPP are more likely to develop glaucoma.[24,25]

Our study investigates whether POAG patients exhibit a decrement in IOP or an increment of OPP after 3 months of aerobic exercise, which guide the clinical treatment of patients with POAG.

Methods

All patients signed informed consent to participate in this study, and the entire study was reviewed and approved by the local ethics committee. All experimental procedures were regulated to adhere to the Declaration of Helsinki of the World Medical Association. The trial was registered in the Chinese Clinical Trial Registry, and the trial registration number was ChiCTR-TRC-10001055 (registration site: http://www.chictr.org http://www.chictr.org).

Study participants

Consecutive Chinese patients between 21 and 70 years of age with POAG were screened. Patients with the presence of glaucomatous optic neuropathy (e.g. as cup-to-disc ratio > 0.6, the asymmetry between eyes ≥0.2, the presence of localized defects of the retinal nerve fiber layer, and/or a neuro-retinal rim in the absence of any other anomalies that could explain such findings), those with the characteristic glaucomatous visual field defect (glaucoma hemifield test results outside normal limits and the presence of at least three contiguous test points within the same hemifield on the pattern deviation plot at P <1%, with at least one at P < 0.5%, excluding points on the edge of the field or those directly above and below the blind spot),[26,27] those with an open-normal appearing anterior chamber angle, and those who locally used prostaglandin analog alone and with morning jog habits or good compliance were included. Key exclusion criteria were patients with secondary glaucoma (pseudo-exfoliation, pigment dispersion, uveitic, traumatic, etc.), those with primary angle-closure glaucoma, one-eyed patients, or those with any previous intra-ocular surgery. Patients diagnosed with coronary heart disease, osteoarthritis, or any systemic condition precluding the practice of physical activity with mild to moderate intensity or patients using any systemic medications (e.g. systemic anti-hypertensive medications) that could affect our result were excluded.

Sample size calculation

Consulting the literature and the results of previous trials,[20-22] the decreasing amplitude of IOP was used to calculate the sample size. The study is powered at 90% with an α (two-sided) of 0.05 to detect an IOP fluctuation between the two groups. Including a 20% dropout rate and the ratio of 1:1 in the exercise group and the control group, the final required sample size was 63 patients in each group.

Randomization

One hundred and twenty-six eligible patients were randomized by a computer (random number method) to receive two interventions. The numbers were placed in non-transparent envelopes and shuffled. Each envelope was opened on the first day of the intervention for each patient. The final sample consisted of 252 eyes.

Measurement

Before the outset of our study, all patients underwent a clinical evaluation of the baseline maximum exercise power using a cycle ergometer. The purpose of this pre-experimental process was to measure the exercise capacity of each patient. The experimental process was composed of two stages: short-term aerobic exercise and long-term aerobic exercise.

At the stage of the short-term exercise, the effect of short-term exercise on IOP and OPP of the two groups was evaluated through the variations of IOP and the changes of OPP after short-term exercise at different levels; meanwhile, we investigated if there is any correlation between the amplitude of variations in IOP and the intensity of exercise. The IOPs were measured by Goldmann applanation tonometry attached to the slit lamp (Mrs, Hagg Strei, Swiss) in the sitting position. The IOPs of both stages were measured throughout by the same technician. The technician was masked to the subjects' groups and stages of intervention. Each measurement of IOP has been performed at least three times automatically. In case readings were unavailable on the display screen, a fourth measurement was performed, considering the mean of the three reliable values.

A cycle ergometer[28-30] (Monark, Stockholm, Sweden) was adapted as a tool for short-term exercise measurements for the subjects. After the patient cycled as fast as possible for 30 seconds, the cycle ergometer reading was defined as the maximum watt. The percentage of a maximum watt (% Wmax) was used to determine the difficulty level of the exercise.

To explore how aerobic exercise affects ocular blood circulation, the OPP mentioned above, systemic blood pressure, and diastolic blood pressure were also measured using a sphygmomanometer (Yuwell).

Intervention

During the clinical evaluation before all experimental stages, patients were required to cycle as fast as possible for 30 seconds to assess each individual's maximum exercise power (Wmax).

One hundred and twenty-six patients with POAG were invited to participate in the study; three declined for the reason that they were not available for follow-up. One hundred and twenty-three patients were randomly assigned into the exercise group (n = 61 cases) and the control group (n = 62 cases). The effect of short-term exercise on IOP of the two groups was measured in two stages: (i) 10 minutes of the cycle ergometer work at 20% Wmax, followed by an interval of 2 minutes to measure IOP, and (ii) 5 minutes of exercise at 60% Wmax, at which point the IOP was measured again. Thus, the IOPs were measured before exercise, after stage 1 and after stage 2, respectively. During the long-term aerobic exercise stage, the exercise group is characterized by regular jogging during 6:00–10:00 every morning. The intensity was observed using a sports watch to reach and maintain the target heart rate range (target heart rate = (220-age) * (0.5-0.7)) for 30 minutes, with the exercise frequency of at least 20 times per month. One course of intervention is offered for 3 months. The control group is designed as a group with irregular exercises. The 24-hour IOPs were measured at the beginning and the end of the long-term exercise stage. All patients were hospitalized and asked not to perform any physical activity upon waking up. All subjects were asked to maintain a supine position for 15 minutes at the beginning of the test. The IOP measurements were taken from 8:00 am to minimize the effect of diurnal variation. The subjects were subjected to IOP recordings at 6:00 am, 8:00 am, 10:00 am, 2:00 pm, 6:00 pm, 10:00 pm, and 2:00 am. These were considered the IOP measurements over 24 hrs under resting conditions. During measurements, the study subjects were asked to rest in the hospital. Before each measurement, one drop of a combination of benoxinate hydrochloride (0.4%) and fluorescein sodium (0.25%) was instilled in the eye. Each IOP measurement was performed at least two times, and a third measurement was taken in the case of more than a 2 mmHg difference, finally taking into account the mean of the two highest values.

Data collection and analysis

Data including age, sex, race, IOP, systolic blood pressure, diastolic blood pressure, exercise watt, heart rate (HR), treatment details, and adverse outcomes were recorded on a datasheet. The primary and secondary outcome measures were IOP and OPP, respectively. Success (i.e. responders) of the short-term study was to reach the exercise intensity of 20%Wmax and 60%Wmax, and the success of the long-term study was to reach and maintain the target heart rate for 30 minutes.

The data were analyzed by statistical software IBM SPSS version 26.0 and GraphPad Prism 9. Non-parametric tests for the two-sample problem (Mann-Whitney U test) were used to analyze age, maximum watt, heart rate, treatment details, IOP, and systolic blood pressure at baseline for the data above that revealed non-normal distribution. An independent-samples T-test was used to analyze diastolic blood pressure for the data that revealed normal distribution. Chi-square tests were used to analyze the differences in the frequency of sex and family history of glaucoma. Non-parametric tests for the two-sample problem (Kruskal–Wallis test) were used to analyze IOP and OPP between pre-exercise and post-exercise at 20% Wmax and 60% Wmax (non-normal distribution). The average IOP values of patients at various time points on 24 hour IOP curves before and after the 3-month study were calculated. An independent-samples T-test was used to analyze the amplitude of variations in IOP values at various time points between two groups (normal distribution). Moreover, intra-group comparisons of 24-hour IOP values were conducted by paired-samples T-tests individually in the exercise and control groups.

Results

Demographic and clinical characteristics of the 246 eyes of 123 subjects (males/females: 62/61, aged 19 to 77 yrs, mean 49 ± 1.1 yrs) are studied. These 126 patients were randomized to receive regular aerobic or optional exercise intervention. Masked examiners observed the target heart rate of all participants. Poor quality exercises were identified in 23 participants and were excluded.

Sixty-one patients in the exercise group and 62 patients in the control group were included in the short-term analysis, and 50 patients in the exercise group and another 50 patients in the control group were included in the long-term analysis [Fig. 1]. There was no statistical significance between the two groups regarding the subject's sex (P = 0.06) and family history of glaucoma (P = 0.36). All patients in this study were Chinese.

The baseline patient and treatment characteristics are shown in Table 1. Characteristics including age (P = 0.33), IOP (P = 0.99), systolic blood pressure (P = 0.13), diastolic blood pressure (P = 0.10), heart rate (P = 0.07), OPP (P = 0.15), and Wmax (P = 0.17) showed no statistical significance between two groups, indicating that patients' baseline levels of the exercise group were approximately on a par with the control group and the parameters were comparable.

Short-term aerobic exercise

Table 2 shows the IOP and OPP after short-term aerobic exercise at different intensities. The IOP of 246 eyes decreased from 19.04 ± 4.77 mmHg to 16.44 ± 4.66 mmHg after 10 minutes of exercise at 20% Wmax with the variation of 2.37 ± 2.67 mmHg. The difference was statistically significant (P = 0.00, Z = -6.16). After another 5 minutes of exercise at 60% Wmax, the IOP further decreased to 13.07 ± 4.28 mmHg with a variation of 5.95 ± 3.80 mmHg. The difference was statistically significant compared with the IOP of pre-exercise (P = 0.00, Z20% Wmax = -13.12) and after 10 minutes of exercise at 20% Wmax (P = 0.00, Z60% Wmax = -8.14). The OPP of individuals increased,

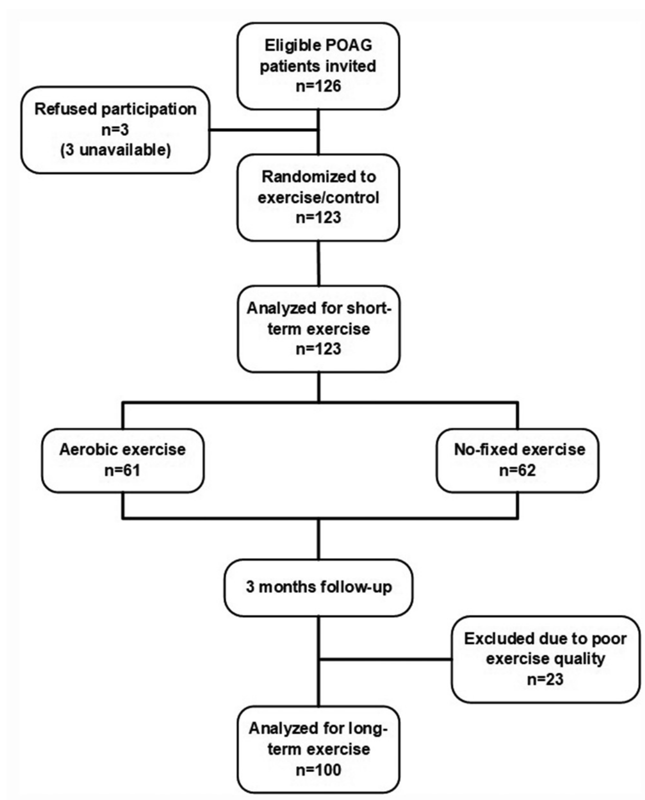

Figure 1: Study flow chart. A top-down flow chart outlines the study process, showing the number of patients (n) with POAG in each step from participation in the study until the end of the long-term study

respectively, from the baseline of 44.36 ± 8.26 mmHg to 46.78 ± 7.49 mmHg and 49.67 ± 8.58 mmHg (P = 0.00). The IOP and OPP levels of the short-term study are illustrated in Figs. 2 and 3.

Long-term aerobic exercise

Table 3 shows the average IOP and IOP variation values of 24 hour IOP levels before and after the 3-month study. From Figs. 4 and 5, the IOP reductions were conspicuously observed at all time points on the 24 hour IOP curve of the exercise group. The difference was statistically significant compared with the IOP variation of the control group (P = 0.002). Intra-group comparisons were also conducted to evaluate the effect of long-term aerobic exercise. The exercise group revealed a positive effect in reducing IOP (P = 0.003), whereas the fluctuation of IOP in the control group showed no discrepancy (P = 0.52).

Responders versus non-responders

Short-term aerobic exercise's success rate reaching the exercise intensity of 20% Wmax and 60% Wmax was 100%. As for the success rate in reaching the HR range, long-term aerobic exercise was successful in 81.97% of patients in the exercise group compared to 80.65% in the control group (P = 0.85). There were no differences in baseline Wmax and heart rate between the responders and non-responders in the two groups (Wmax: exercise group P = 0.63, control group P = 0.53. HR: exercise group P = 0.35, control group P = 0.24).

Table 1: Baseline characteristics and treatment parameters in the two groups

Parameter	Exercise group (*n*=61)			Control group (*n*=62)			*P*
	Median (mean)	IQR (SD)	Range (min to max)	Median (mean)	IQR (SD)	Range (min to max)	
Age	52 (49.83)	42, 58 (1.5)	21-70	47 (47.48)	39, 57 (1.6)	22-67	0.33
IOP	18 (18.98)	16, 22 (0.38)	12-33	18.5 (19.1)	16, 22 (0.48)	10-43	0.99
Systolic blood pressure	129 (129.08)	120, 139 (1.85)	100-160	122.5 (125.07)	111.75, 135 (2.03)	101-167	0.13
Diastolic blood pressure	80 (80.39)	74, 89 (1.26)	58-105	76 (77.37)	70, 83.5 (1.29)	60-100	0.10
HR	72 (73.84)	67.75, 78.5 (1.28)	57-100	75 (76.19)	71, 81.25 (1.44)	48-114	0.07
OPP	46 (45.6)	40.64, 50.61 (0.93)	28.89-64.22	44.22 (43.04)	38.83, 48.67 (1.21)	11.22-59.78	0.15
Wmax	225 (219.6)	151, 294 (8.65)	80-294	199 (204.9)	159, 240 (7.38)	70-294	0.17

Age, in years; Diastolic blood pressure, in mmHg; HR, heart rate, in bpm (beat per minute); IOP, intra-ocular pressure, in mmHg; IQR, inter-quartile range; *n*, number of patients in each group; OPP, ocular perfusion pressure; SD, standard deviation; Systolic blood pressure, in mmHg; Wmax, maximum exercise power, in Watt

Table 2: The IOPs at baseline, after 10 min of exercise at 20% Wmax, and after 5 min of exercise at 60% Wmax

Exercise intensity	IOP (*n*=246)			*P*	OPP (*n*=246)			*P*
	Median (mean)	IQR (SD)	Range (min to max)		Median (mean)	IQR (SD)	Range (min to max)	
Baseline	18 (19.04)	16, 22 (4.77)	10-43	0.00	45.11 (44.36)	39.78, 50.22 (8.26)	11-64	0.00
20% Wmax for 10 mins	16 (16.44)	13, 18.75 (4.66)	7-46		46 (46.78)	42.17, 51.69 (7.49)	29-68	
60% Wmax for 5 mins	12 (13.07)	10, 16 (4.28)	4-38		50.22 (49.67)	45.08, 53.42 (8.58)	11-93	

IOP, intra-ocular pressure, in mmHg; IQR, inter-quartile range; *n*, number of treated eyes in each group; OPP, ocular perfusion pressure; SD, standard deviation; Wmax, maximum exercise power, in Watt

Table 3: The average IOP/IOP variation values of 24 h IOP levels before and after the 3-month study

Parameter	IOP/Variation in IOP (in average)							*P*
Time points	6:00 AM	8:00 AM	10:00 AM	14:00 PM	18:00 PM	22:00 PM	2:00 AM	
Exercise group (*n*=50)								
IOP at baseline of the 3-month treatment*	18.21	18.41	17.98	17.22	18.09	18.31	19.32	0.003
IOP at end of the 3-month treatment	19.61	18.61	19.24	18.12	18.75	18.68	20.14	
Control group (*n*=50)								
IOP at baseline of the 3-month treatment*	21.03	19.21	19.61	18.05	18.16	17.87	21.16	0.523
IOP at end of the 3-month treatment	20.59	19.68	19.46	18.58	17.51	17.73	20.73	
IOP variation								
Exercise group	1.40	0.20	1.26	0.90	0.66	0.37	0.82	0.002
Control group	-0.44	0.47	-0.15	0.53	-0.65	-0.14	-0.43	

AM, ante-meridiem; IOP, intra-ocular pressure, in mmHg; *n*, number of patients in each group; PM, post-meridiem. *There is no statistical significance between 24 h IOP at baseline in the exercise group and the control group

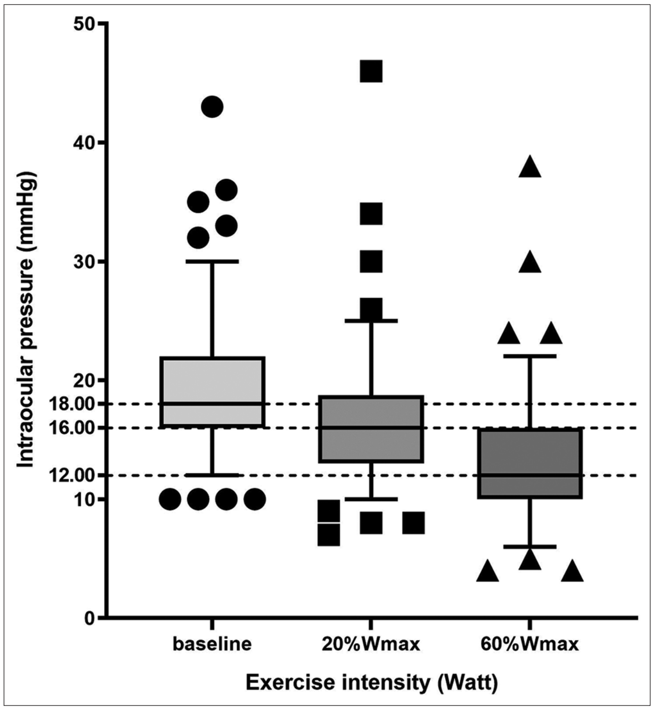

Figure 2: The IOP of 123 subjects after short-term aerobic exercise at intensities of 20% Wmax and 60% Wmax (Wmax = maximum watt)

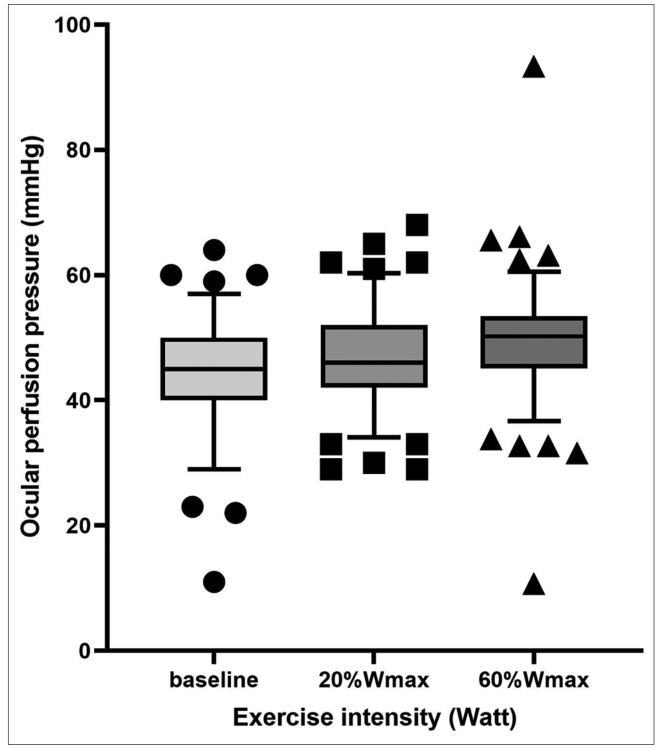

Figure 3: The OPP of 123 subjects after short-term aerobic exercise at intensities of 20% Wmax and 60% Wmax (Wmax = maximum watt)

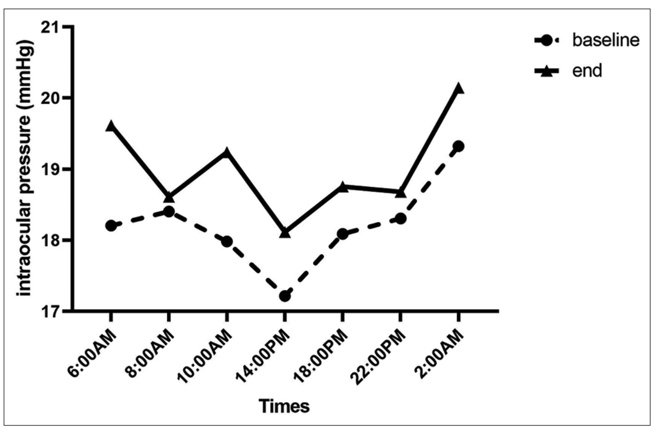

Figure 4: The 24 hour IOP level in the long-term exercise group before (baseline) and after (end) 3 months of exercise

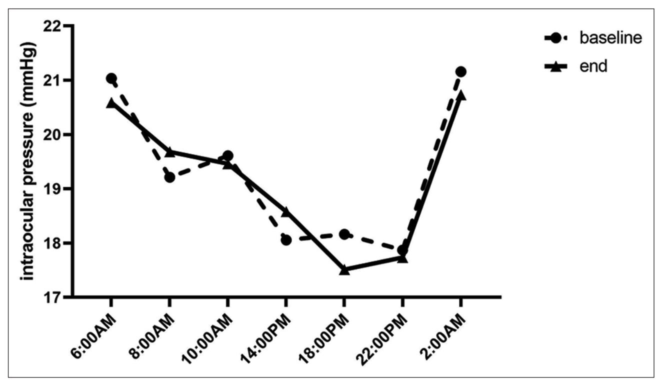

Figure 5: The 24 hour IOP level in the long-term control group before (baseline) and after (end) 3 months of exercise

Discussion

Our study investigates the effect of short-term and long-term aerobic exercise on IOP and OPP of POAG patients. As a type of dynamic exercise, aerobic exercise has diversified forms, including walking, jogging, cycling, and so on. The exercise method was adopted because it had been widely proved[14-16] that dynamic exercise could decrease IOP. The loss of sweat and water during exercise duration leads to the aggrandizement of the colloidal osmotic pressure of plasma which decreases the production of aqueous humor (AH).[31] As a consequence, the reduction of AH production can significantly diminish the IOP level.[32,33]

The short-term study was accomplished with a cycle ergometer. This exercise tool is considered one of the Watt quantification tools. After 10 minutes of moderate (20% Wmax) exercise, 123 subjects had a significant IOP decrease (2.37 ± 2.67 mmHg) ($P = 0.00$). The exercise intensity is equivalent to a brisk walk in our daily lives. Karabatakis *et al*.[21] reported that the post-exercise IOP decrease in normal people was 1 to 8 mmHg, whereas Qureshi[22] reported that glaucoma patients could have a 12.86 ± 2.05 mmHg post-exercise IOP decrease. Previous research has demonstrated that the IOP decreased after exercise and was strongly correlated to the exercise intensity.[15] To determine whether subjects have a larger IOP decrease after heavy exercise (equivalent to rapid running), we implemented a heavy cycling exercise (60% Wmax) for 5 minutes after moderate exercise. Meaningful results were found, indicating that subjects had a significantly greater post-exercise IOP decrease (5.95 ± 3.80 mmHg) ($P = 0.00$). Moreover, the decreasing amplitude in IOP after exercise was negatively correlated with baseline IOP (r = -0.522, P = 0.00). The higher the baseline IOP was, the greater IOP decreased after exercise. The decreasing amplitude in IOP was also negatively correlated with heart rate during exercise (r = -0.217, P = 0.023). The faster the heart rate was during exercise, the greater IOP dropped after exercise. Strong evidence from several studies has shown that the heart rate can reflect the intensity of exercise.[34] Moreover, the excitement of the sympathetic system and simultaneous inhibition of the para-sympathetic system during exercise are suggested to raise the heart rate.[35]

It is also found that the OPP of the eyes increased significantly after low-intensity and high-intensity exercise, which is beneficial to POAG patients. Research indicates that insufficient ocular perfusion and pathological elevation of the IOP level are the main factors of glaucoma. Individuals with low OPP have a higher risk of developing glaucoma.[24,25] The neuro-degeneration of retinal ganglion cells leads to visual loss. However, physical exercise can enhance neuronal plasticity[36] to protect retinal ganglion cells and show resistance to neuro-degeneration of retinal degenerative diseases such as glaucoma.[37-39]

According to the long-term study, the 24 hour IOP curve of the control group was highly consistent in trend, and there was no significant difference in IOP at each time point before and after 3 months. However, it has been observed in the exercise group that the 24 hour IOP level after 3 months of long-term exercise was generally lower than that at baseline. The decline was obvious at all time points on the 24 hour IOP curve, especially at 6:00 am and 10:00 am, which may be why our 3-month exercise time was scheduled from 6: 00 to 10: 00 in the morning. Furthermore, for each 1 mmHg higher long-term IOP fluctuation, a 31% higher risk of glaucomatous visual field loss progression is associated.[40,41] It may be inferred that long-term aerobic exercise helps reduce IOP while protecting the optic nerve of POAG patients.

The decrease in IOP after exercise is also affected by multiple factors. It is found that men generally have a greater decreasing amplitude of IOP after exercise than women, considering that the exercise intensity of men is generally greater than that of women.[42] It is also found that those with no family history had a more apparent decrease than those with a family history, considering that those with a family history of glaucoma have larger intrinsic stiffness of trabecular functions.[43]

Considering the better accuracy and precision, we chose the Goldmann applanation tonometer as a tool for IOP measuring. However, there are still several limitations in this study: (i) taking IOP measurements seven times in 24 hours may result in cornea epithelium injury; (ii) the long duration of IOP measurements, especially at night, may affect the resting; and (iii) theoretically, sample size may not be adequate.

Conclusion

In conclusion, short-term and long-term aerobic exercise may reduce IOP in POAG patients. The decrement of IOP and increment of OPP after short-term aerobic exercise are related to the exercise intensity. Furthermore, long-term aerobic exercise may be beneficial for protecting the optic nerve of POAG patients. The study suggests that appropriate aerobic exercise is recommendable in treating POAG patients clinically.

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Conflicts of interest

There are no conflicts of interest.

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