Twenty-four Hour Monitoring of Intraocular Pressure and Blood Flow of the Optic Nerve Head in Normal Tension Glaucoma and Primary Open -Angle Glaucoma Patients

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Twenty-four Hour Monitoring of Intraocular Pressure and Blood Flow of the Optic Nerve Head in Normal Tension Glaucoma and Primary Open -Angle Glaucoma Patients

Directed by Professor Chan Yun Kim

The Master's Thesis submitted to the Department of Medicine, the Graduate School of Yonsei University in partial fulfillment of the requirements for the degree of Master of Medical Science

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This certifies that the Master's Thesis
of Kyoung-Tak Ma is approved.

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ABSTRACT

Twenty-four hour monitoring of intraocular pressure and blood flow of the optic nerve head in normal tension glaucoma and primary open–angle glaucoma patients

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The measurement of intraocular pressure is essential in the diagnosis and management of glaucoma but a single measurement in the ophthalmologist's office may or may not reflect what the IOP is at other times of the day or night. This study was designed to characterize the 24-hour pattern of intraocular pressure (IOP), blood pressure(BP) and blood flow of the optic nerve head (ONH) in previously-diagnosed patients. Thirty one POAG patients and thirty nine NTG patients were enrolled in the examination. Measurements of IOP and blood pressure were taken every two hours during a 24-hour period from the normal-tension glaucoma (NTG) group and the primary open-angle

glaucoma (POAG) group. Blood flow of the ONH was measured at 2 p.m., 10 p.m. and 6 a.m.

The mean diurnal IOP in both the sitting and supine positions were higher in the POAG group than in the NTG group. Mean ocular perfusion pressure results were higher in the NTG group than in the POAG group. We measured the blood flow of the ONH three times and found that the flow was the lowest when measured at 10 pm. NTG patients had higher results at all three measurements.

To our knowledge, this is the first attempt to address the association between diurnal IOP, BP and blood flow of the ONH. Diurnal IOP was higher in the POAG group than in the NTG group and although blood pressure and blood flow of the ONH did not correlate with IOP in a statistically significant manner, ocular blood flow was lowest at 10pm.

Key words: Diurnal IOP, Blood pressure, Ocular blood flow, primary open-angle glaucoma, normal-tension glaucoma

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I. INTRODUCTION

Glaucoma is a degenerative optic neuropathy characterized by optic nerve head (ONH) changes and visual field loss often related to increased intraocular pressure (IOP). It has been unequivocally shown that an elevated IOP is a risk factor for the development of glaucomatous damage and that IOP reduction offers therapeutic benefits to glaucoma patients. Elevated IOP is the only proven risk factor associated with glaucomatous optic neuropathy, and the lowering of IOP is the only proven treatment for the condition.

There for measurement of IOP by the ophthalmologist is very important. However, many patients continue to experience visual field loss despite adequate IOP control, and this has prompted the search for alternative treatment strategies. Factors other than IOP are likely to have a role in the pathogenesis of glaucomatous optic neuropathy, particularly in individuals with normal-tension glaucoma (NTG). In the present study, we collected 24-hour data on IOP and blood pressure (BP) and blood flow of the optic nerve head (ONH) in NTG and primary open-angle glaucoma (POAG) patients. NTG is typically diagnosed in patients who have optic disc and/or visual field glaucomatous changes but who have never had an untreated intraocular pressure (IOP) above 21 mmHg. In Western countries, the incidence of NTG is believed to be generally much lower than that of POAG.[2] In Japan, however, Shiose and associates found NTG in 2.04% of the adult population, while POAG was diagnosed in only 0.58% of adults.[2] A similar distribution has been noted in Korea.[3] These two countries may have a similar incidence of NTG because of their historically close genetic ties. However, the reason why Japanese and Koreans would have a higher incidence of NTG is not specifically known. Wu and associates reported that corneal thickness is lower in the normal Japanese population (517.5 ± 29.8 μm) compared to that found in Western populations.[5]

Thinner corneas might allow for falsely lower readings by Goldmann tonometry, which explains at least some of the lower IOP readings in Japanese patients with glaucoma.[6] However, working specifically in the Japanese glaucoma population, Tang and co-workers found no differences in corneal thickness between NTG (548 ± 33 μm) and POAG patients (550 ± 33 μm).[7] It is possible that genetic differences could play a role in the higher incidence of NTG in Korea and Japan.[8,9] However, these potential differences have not been completely defined.[9-11]

Clinical differences between NTG and POAG patients in Japan and Korea are not well described. Nakatsue and coworkers found no differences in optic disc morphology in Japan between NTG and POAG patients.[12] However, Yang and Park noted that a larger optic disc was found in NTG patients than in POAG patients in Korea.[13]

Blood flow in any tissue is generated by the perfusion pressure that is defined as the difference between mean arterial pressure (MAP) and venous pressure. In the eye, the venous pressure should be marginally higher than the intraocular pressure (IOP) to allow for adequate blood circulation. In this study we compared the IOP of the two previously-diagnosed glaucoma groups and investigated whether there was a statistically significant association between diurnal IOP and BP and blood flow in the ONH.

II. MATERIALS AND METHODS

The study adhered to the tenets of the Declaration of Helsinki and was approved by our Institutional Review Board. Thirty-one patients (M:17, F:14) who were diagnosed with POAG and 39 patients who were diagnosed with NTG (M:21, F:18) were recruited into this study. The average age was 43.9 years in the POAG group and 48.8 years in the NTG group. The diagnosis of NTG or POAG was made by a single glaucoma specialist (YJH). All of the patients had been previously-diagnosed with glaucoma and most were using intraocular lowering agents. Unlike previous studies, we did not stop the medication or have a washout period but instead had the patients continue to use the medication.

Intraocular pressure was measured every two hours in a supine position and in a sitting position. Blood pressure was also measured every two hours in a supine position. Blood flow of the ONH was measured at 2 p.m., 10 p.m. and 6 a.m. using a Heidelberg Retinal Flowmeter (HRF).

Blood flow in any tissue is generated by the perfusion pressure that is defined as the difference between mean arterial pressure (MAP) and venous pressure. In the resting position, MAP is calculated as:

$$MAP = DBP + \frac{1}{3}(SBP - DBP)$$

where the difference between the systolic (SBP) and diastolic (DBP) blood pressures is the pulse pressure. In the eye, the venous pressure should be marginally higher than the intraocular pressure (IOP) to allow for adequate blood circulation. Therefore, to calculate the mean ocular perfusion pressure (MOPP), IOP is substituted for the venous pressure.

$$MOPP = \frac{2}{3}MAP - IOP$$

IOP and BP and blood flow in the ONH were each measured by a single doctor to eliminate bias caused by a difference of examiners.

Three participants (two NTG patients and one POAG patient) dropped out during the examination because of ocular discomfort due to corneal erosions. HRF was used to measure the optic disc blood flow. One examiner measured all the patients and the data were analyzed using the Automatic Full-Field Perfusion Image Analyzer (AFFPIA) program, and the ‘average flow’ was calculated. The conventional method, which uses a sampling technique in a 10x10 pixel frame, varies according to the selection of the pixels. (Fig.1) AFFPIA uses two circles with one just in the margin of the optic disc and the other one just outside the optic pit to analyze the blood flow.

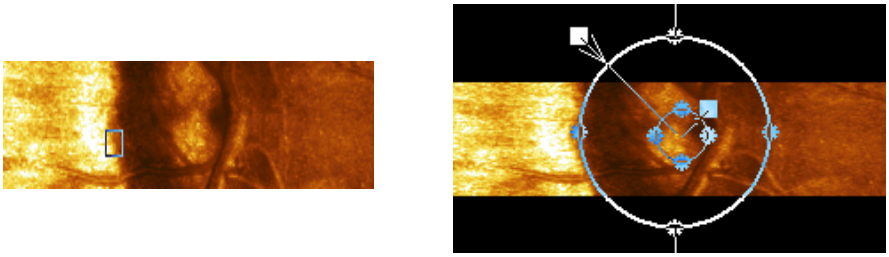

Figure 1: Conventional 10x10 pixel frame method (left) vs. automatic full-field perfusion

For statistical analysis, we used the SPSS®12.01(SPSS Inc., Chicago ,IL) for Windows program. The numerical variables were subjected to an independent samples t-test. The level of statistical significance was set at $P<0.05$. [14-16]

III. RESULTS

Thirty-one patients (M:17, F:14) who were diagnosed with POAG and 39 patients who were diagnosed with NTG (M:21, F:18) were recruited into this study. Three participants (two NTG patients and one POAG patient) dropped out during the examination. The diurnal curve of intraocular pressure in NTG and POAG patients produced results in correlation with previous reports. The average number of medication was 1.82±0.98 in the POAG group and 1.04±0.75 in the NTG group. ($P<0.05$) The average central corneal thickness (CCT) was 557.35±32.2 um in the POAG group and 539.05±36.29 um in the NTG group.[17-19] ($p=0.076$) The average MD of the latest visual field exam was -10.52±8.27 in the POAG group and -6.42±6.81 in the NTG group.($P<0.05$)

Table 1. Baseline demographic data of patients

	NTG	**POAG**	**p value**
Gender	Male 21; Female 16	Male 17; Female 13	
Age	48.8±13.3	43.9±13.4	p=0.16
Medication	1.04±0.75	1.82±0.98	p<0.05
Central corneal thickness (um)	539.05±36.29	557.35±32.2	p=0.076
Mean deviation (dB)	-6.42±6.81	-10.52±8.27	p<0.05

The mean sitting and supine IOP, MAP and MOPP results of the two groups are summarized in Table 2.

Table 2. Patients Demographics and Parameters of IOP, MAP and MOPP

	NTG	**POAG**	**p value**
Sitting IOP (mmHg)			
Diurnal period (6am-12am)	12.46±2.19	14.96±3.61	p<0.05
Nocturnal period (2am-4am)	17.41±3.73	20.15±5.67	p<0.05
Supine IOP (mmHg)			
Diurnal period (6am-12am)	16.535±3.22	18.86±4.19	p<0.05
Nocturnal period (2am-4am)	17.41±3.73	20.15±5.67	p<0.05
Mean arterial pressure (supine)	86.6±10.1	85.8±11.2	p=0.29
Mean ocular perfusion pressure	41.12±7.15	38.18±7.22	p<0.05

When comparing the two groups, the NTG group had a lower IOP than the POAG group (Fig. 2). The diurnal variation (the difference between maximum and minimum) of sitting IOP was 4.0±2.82 mmHg in the POAG group, which was significantly larger than the variation in the NTG group (3.51±2.17, $p > 0.05$). The variation in diurnal, supine IOP was also larger in the POAG group than the NTG group. (6.91±2.60, 6.58±2.49 $p > 0.05$).

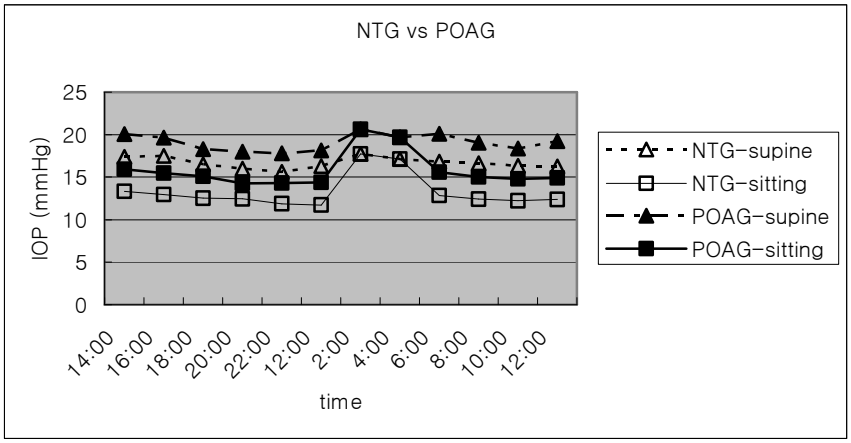

Figure 2. Profile of 24-hour intraocular pressure(IOP) variation in NTG and POAG patients. Solid symbols represent IOP of POAG patients and open symbols IOP of NTG patients. Squares representing sitting IOP, and triangles, supine IOP

In the POAG patients, the MAP did not have a statistically significant correlation with the IOP (p=0.066), but the MAP in NTG patients showed a statistically significant correlation with the IOP (p=0.000).

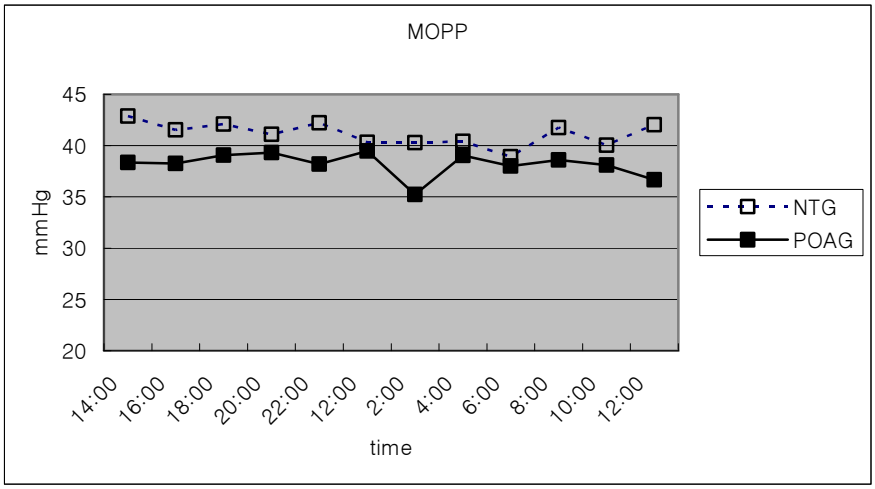

Figure 3. Comparing Mean ocular perfusion pressure(MOPP) between NTG group and POAG group

Diurnal MOPP of the two groups were calculated using the diastolic and systolic blood pressures and the IOP (Fig. 3). In all measurements, the NTG patients showed higher values and the data at 2 p.m. (p=0.019), 10 p.m. (p=0.026), 2 a.m. (p=0.006) and 12 p.m. (p=0.02) showed statistically significant differences among the two groups.

Blood flow of the ONH in the two groups is shown in Figure 4. Data were higher in the POAG group in all three measurements. We measured the blood flow of the ONH three times and found that the flow was lowest at 10 pm. NTG patients had higher results at all three measurements

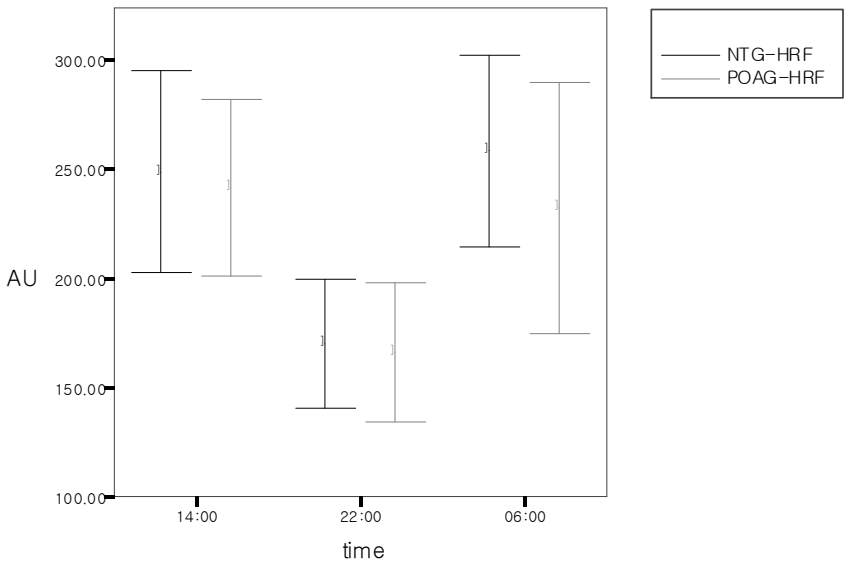

Figure 4. Comparing blood flow of optic nerve head between NTG group and POAG group

IV. DISCUSSION

The definition of glaucoma has changed through the years, and there has also been a continuous effort to identify significant risk factors for the condition. [20-22] An increased IOP is the most important risk factor for the disease, and several studies have clearly identified that a high IOP is associated with both the progression of glaucoma and the conversion of ocular hypertension to open-angle glaucoma. [23,24]

Recently, there has been increasing interest in ocular blood flow with the progression of glaucoma since many patients continue to experience visual field loss despite adequate IOP control and also medication related to the blood flow. [25-29]

Autoregulation is the physiologic phenomenon in which the local arteriolar resistance changes dynamically to keep tissue blood pressure at a relatively constant level that is determined by local metabolic activity despite changes in MAP and perfusion pressure. The mechanism has not been fully explained but it is believed that NTG patients are more easily influenced than POAG patients. In this study, NTG patients had a higher MOPP than did their POAG counterparts, and at four measurements these differences were statistically significant.

To our knowledge, this is the first attempt to address the association between IOP, BP and blood flow of the ONH. We measured the blood flow of the ONH three times and found that the flow was lowest at 10pm compared to 6am and 2pm. NTG patients had higher results at all three measurements.

Unlike previous studies, patients of this study had been previously diagnosed with glaucoma and were using IOP-lowering eye drops. We did not ask them to discontinue the use of these drops due to ethical problems that could occur when asking a patient to stop medication for study purposes.[30]

The patients were not advised to stop and go through a washout period; instead they were advised to use their medication as they had before they were recruited into the study. We thought that our study could measure the diurnal change in IOP of patients who are continuously taking their IOP-lowering medication.[31] However, the diurnal changes were similar to the findings of previous studies, in both groups. Because the duration of the effect of eye drops differs among the diverse kinds of medication and the fact that its effect on ocular blood flow is controversial, we did not take these matters into consideration.

Age and central corneal thickness of the two groups did not show statistically significant difference but, medication and mean deviation of visual field examination between the two groups showed significant

difference.

We understand that more frequent measurements of the HRF would have produced more significant diurnal ocular blood flow results, but due to realistic difficulties we were only able to measure the HRF three times: at 2 p.m., 10 p.m. and 6 a.m. In future studies, more frequent measurements would have more practical values.

V. Conclusion

Knowledge of the diurnal IOP curve of a patient with glaucoma provides valuable information to the ophthalmologist treating the patient. Knowing the peak IOP, the time it occurs, and the range of diurnal fluctuation may allow the ophthalmologist to tailor a better treatment regimen for the patient.

In this study, we evaluated the diurnal curve of IOP, BP and blood flow of ONH in glaucoma patients using IOP lowering medication.

Further investigation to find the relationship between IOP, MOPP and blood flow of the ONH would be worthwhile in finding significant risk factors for the diagnosis and treatment of glaucoma.

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국문요약

정상 안압 녹내장과 개방각 녹내장 환자에서의 24 시간 안압 및 안혈류 측정

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마 경 탁

안압의 측정은 녹내장의 진단 및 치료에 있어서 필수적이지만 24 시간 동안 안압이 주기적으로 변하는 것이며, 진료 시간에 일회 측정한 안압으로는 피검자의 안압 상태를 정확히 파악할 수 없으므로 안압의 일차변동 측정이 필요하다. 본 연구에서는 정상 안압 녹내장과 개방각 녹내장 환자에서 안압의 24 시간 측정을 통해 일교차를 측정하고 동시에 혈압과 안혈류를 측정하여 서로간의 상관 관계를 찾아 보고자 하였다.

31 명의 개방각 녹내장 환자와 39 명의 정상 안압 녹내장 환자들을 대상으로 하였으며 안압과 혈압은 두 시간마다 측정하였고 안혈류는 오후 2 시, 10 시 그리고 아침 6 시에 측정하였다.

평균 안압은 개방각 녹내장 환자에서 정상 안압 녹내장 환자보다 항상 높게 측정되었다. 평균 안구 관류압은 정상 안압 녹내장에서 항상 개방각 녹내장보다 높게 측정되었다. 시신경 유두에서의 혈류는 세 차례 측정되었으며 밤 10 시에 가장 낮게 측정되었다.

본 연구는 안압, 혈압 그리고 시신경 유두에서의 혈류간의 일차 변동을 측정하고 서로 간의 상관 관계를 찾고자 하였다. 본 연구에서는 여러 인자 상호 간에 밀접한 상관 관계를 찾지 못했지만 앞으로의 지속적인 연구가 의미 있을 것으로 생각된다.

핵심되는 말: 안압 일차 변동, 혈압, 시신경에서의 안혈류, 개방각 녹내장, 정상 안압 녹내장