ORIGINAL ARTICLE

Effects of Arterial Stiffness on Visual Field Severity and Progression in Malay Patients with Primary Open Angle Glaucoma

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ABSTRACT

Introduction: Vascular dysregulation is postulated to be involved in the pathogenesis of primary open angle glaucoma (POAG). Systemic arterial stiffness may accelerate the pre-existing damage. The purpose of this study was to determine the association of arterial stiffness with severity and progression of visual field in Malay patients with POAG. **Methods:** A cross-sectional study was conducted with 55 patients with POAG and 55 age- and sex-matched control subjects. The patients with POAG were further divided in accordance with their Advanced Glaucoma Intervention Study (AGIS) scores on their visual fields (VFs) (mild in 23 patients, moderate in 18, and severe in 14). Progression was defined as the worsening of the VF defect quantified as an increase in AGIS score of 4 points from the baseline. Arterial stiffness was measured using SphygmoCor and quantified as pulse wave analysis (PWA) and pulse wave velocity (PWV). **Results:** No significant differences in PWA and PWV were found between the patients with POAG and the control subjects (p=0.333 and p=0.443, respectively). The mean follow-up duration for the patients with POAG was 4.7±3.1 years. PWA and PWV showed no significant association with POAG severity after the confounding factors were controlled for. Ten patients with progression of VF were identified. In the analysis of covariance, a significantly higher PWV was found in the patients with disease progression (p=0.036). **Conclusion:** VF severity and progression were not associated with systemic arterial stiffness. The probable reason is that other factors affecting retinal microcirculation may play a larger role in the severity and progression of POAG.
Malaysian Journal of Medicine and Health Sciences (2022) 18(4):27-34. doi:10.47836/mjmhs18.4.5

Keywords: Arterial stiffness, Severity, Progression, AGIS score, Primary open angle glaucoma

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INTRODUCTION

Glaucoma is recognised as the second leading cause of blindness worldwide (1) and is the main cause of global irreversible blindness (2). Glaucoma belongs to a group of optic neuropathies involving progressive degeneration of retinal ganglion cells, which leads to cupping of the optic disc (3) and visual field defect frequently associated with increased intraocular pressure (4). The pathogenesis of glaucoma is still unclear but is believed to be multifactorial (5).

The mechanical theory of the pathogenesis of glaucoma postulates that direct strain on the eye by high intraocular pressure (IOP) causes the optic neuropathy in glaucoma (6). However, a well-controlled IOP does not always mean that the glaucoma is arrested, as progression has been observed in many cases (7). Therefore, the disease could be attributable to other factors. Another renowned hypothesis is the vascular theory that proposes that inadequate blood supply leads to the sequelae of glaucomatous optic neuropathy (8). Vascular regulatory dysfunctions, namely vasospasm and atherosclerosis, may contribute to the reduction of ocular blood flow (9,10). Autoregulation plays an important role in maintaining adequate ocular perfusion in spite of changes in local vascular parameters. Loss of such ability will result in vascular dysregulation (5).

Arterial stiffness is defined as reduced elasticity of the artery which renders the vessel unresponsive to changes in intravascular pressure (11). This elasticity is crucial in ensuring a smooth stream of blood from cyclical ventricular ejection during its delivery to the end organs (12). As the artery becomes less distensible, the

diastolic blood pressure (dBP) declines, and the pulse pressure widens. This confers to patients higher risks of developing heart problems and other organ impairments including the eye (11,13). Arterial stiffness increases with age owing to the degeneration of elastic fibres with aging (14). Age is also a primary risk factor of glaucoma and greatly influences disease progression, which further supports the vascular theory of glaucoma (15,16).

Arterial stiffness can be quantified using various techniques, among which the use of SphygmoCor is considered the non-invasive gold standard. SphygmoCor is a non-invasive high-fidelity automated tonometer (17). It was developed on the basis of the principle that the stiffness of an artery can be represented by the speed of the blood pressure (BP) waveform of the pulse that passes in the aorta. Anatomically, all vessels are connected to the aorta, measuring aortic stiffness may predict the blood supply to the end organ including the eye. That is, the higher the velocity, the stiffer the aorta (18). SphygmoCor records the pressure wave velocity (PWV) in a section of an artery and performs pulse wave analysis (PWA) (19,20).

Deranged microcirculation, excitotoxicity, altered immunity, and oxidative stress are the postulated pathogenic mechanisms of glaucoma (3). The extent of involvement of arterial stiffness in the development of glaucoma is still controversial (5). In their study, Siasos et al found that patients with primary open angle glaucoma (POAG) showed pronounced endothelial dysfunction, significant arterial stiffness, and marked inflammation (19). On the contrary, Graham and colleagues did not find a significant association between systemic arterial stiffness and glaucoma in their study (17). Meanwhile, Chiba and colleagues found a similar finding in Asian populations (20).

The presence of compromised blood supply may accelerate the progression of optic neuropathy in patients with glaucoma (21). However, no specific study has investigated the correlation between arterial stiffness and the severity and progression of glaucoma. The aim of the present study was to investigate whether associations exist between the indices of arterial stiffness and the visual field severity and progression in patients with glaucoma. The potential differences in these indices between patients with glaucoma and control subjects were also examined.

MATERIALS AND METHODS

Patient recruitment

This cross-sectional study was conducted on 55 patients with POAG who were admitted between July 2012 and November 2014 in Hospital Universiti Sains Malaysia (HUSM), Kelantan, Malaysia. This study received ethical approval from the Human Research Ethics Committee, Universiti Sains Malaysia (reference no. USMKK/PPP/JEPEM [234.3(12)]), and was conducted in accordance with the guidelines for human research set forth in the Declaration of Helsinki. This study was partially funded by the Universiti Sains Malaysia Research University Individual Grant 1001/PPSP/812101. The sample size was calculated using the Power and Sample Size programme version 3.0.43. The statistical power was set at 80% with standard deviation of 2.07m/s and expected difference of 1.26m/s of SphygmoCor reading (19). Based on the objective, the sample size required was 43 patients with POAG and 43 control subjects. The minimum required sample size after considering a 10% dropout rate was 100.

A total of 110 Malay patients (55 patients with POAG and 55 control subjects) were recruited in this study. The recruitment was conducted by an investigator who was blinded to the other procedures performed on the patients. Non-probability sampling was conducted among the Malay patients with POAG who attended the glaucoma clinic in HUSM between July 2012 and November 2014. Subjects for the control group were selected among patients who had an uncomplicated cataract surgery, a pterygium surgery, and dry eyes. The control subjects were recruited after enrolment of patients with glaucoma to ensure that age and sex matching between the two groups. POAG was defined as the presence of structural damage at the optic nerve head and glaucomatous visual field defect in an eye with an open angle on gonioscopic examination and an IOP > 21 mmHg at initial diagnosis (22). Malay was defined in accordance with Article 160 of the Malaysian Federal Constitution (23). A pedigree chart was drawn for individual patients to ensure that no interracial marriage existed for at least three generations. Patients who were unable to provide a complete pedigree chart were excluded.

A thorough ocular examination was performed to confirm the diagnosis of POAG and to exclude glaucoma or suspected glaucoma in the control subjects. The Humphrey visual field analyser (HFA; Carl Zeiss, Meditec Inc, USA) with the Swedish Interactive Threshold Algorithm standard 24-2 strategy was used for both patients' groups. The medical records of the recruited patients were reviewed for information on the IOP at each follow-up visit. Patients with IOPs ≤ 18 mmHg throughout the follow-up period were included in the study. They were deemed to have achieved the target pressure.

From the medical records, two consecutive reproducible and reliable visual fields obtained using the HFA at the initial diagnosis were included in the study. Patients with non-reliable and non-reproducible visual fields at the initial diagnosis were excluded from the study. Only those with two reliable and reproducible visual fields in at least one eye based on reliability indices (<20% fixation loss, <33% false positive error, and <33% false

negative error) were included. A total of 123 patients were recruited at the beginning of the recruitment period (65 patients with POAG and 58 control subjects).

All recruited subjects were required to conduct another two consecutive visual fields using HFA within three months post recruitment period. They were given three attempts to provide two reliable and reproducible visual fields. Three patients with POAG were excluded owing to the non-reliable visual field obtained after three attempts. Another three control subjects were also excluded owing to a similar issue, while seven patients with POAG were excluded because no two reliable and reproducible visual fields were obtained at the initial diagnosis.

Subjects (patients with glaucoma and control subjects) had to have visual acuities better than 6/60 in at least one eye to be included in the study. Any patients with an underlying refractive error of >−3.0 dioptres, media opacity (e.g. corneal opacity and vitreous haemorrhage), and concurrent ocular disease, including visually significant cataract and pterygium, were excluded. Refractive error of >-3.0 dioptres affects the accuracy of HFA especially with the presence of tilted disc. Those with a history of glaucoma filtering surgery and ischemic heart disease were also excluded.

Advanced Glaucoma Intervention Study Score for glaucoma severity and progression

The Advanced Glaucoma Intervention Study (AGIS) score was applied to four reliable and reproducible visual fields to group the patients according to severity and determine disease progression (24). The AGIS scoring was applied for numerical score (actual score) but the categorical severity of glaucoma was modified as : mild, 0–5; moderate, 6–11; and severe, 12–20 (25,26). In this modified categorical severity, the early and end-stage were combined as mild and severe respectively (25,26). Severity was assessed on the basis of the two most recent visual fields obtained using the HFA. Glaucoma was assessed as progressive when the difference in AGIS score was ≥4 points (24). Scoring for the progression was based on the results of two HFA tests at the initial diagnosis of POAG and two recent HFA tests.

HFA scoring was performed independently by two investigators, who were blinded to each other's scoring, at different times and locations. The mean of the two scores was recorded to establish the severity and progression of glaucoma. If both eyes were eligible for HFA assessment, only the right eye was chosen regardless of severity.

Arterial stiffness measurement

The recruited patients with glaucoma and controls were scheduled for arterial stiffness measurement using SphygmoCor (Atcor Medical, Australia) in the Vascular Laboratory, School of Medical Sciences, Universiti Sains Malaysia. On the appointment date, they were asked to fast for 6 to 8 hours before and avoid caffeine on the night before and smoking a week before the procedure and wear loose clothing during measurement. Upon arrival, with clothes on, the patient's height and weight were measured by the staff nurse using a digital scale (Seca, Germany). Body mass index (BMI) was calculated, and BP was measured using an automatic BP set (Terumo, Japan), with the patient in supine position. Two measurements were taken, and the mean was recorded. Venesection was performed to evaluate the patients' fasting lipid profiles (FLPs) and fasting blood glucose levels.

The primary investigator, who was blinded to the recruitment process and modified AGIS scoring, was responsible for measuring arterial stiffness. The SphygmoCor system is composed of a desktop PC, a tonometer probe, an electronic module, and a footswitch. In this system, the peripheral arteries, mainly the carotid, femoral, or radial artery, are flattened between the probe and the underlying structure. With the patient in supine position, three electrocardiographic leads (Atcor Medical) were placed, one each at the apex, fifth intercostal space, and second intercostal space of the left side of the chest. The radial pulse of the subject was identified. The SphygmoCor probe was then placed at the radial artery to obtain the waveform, and measurements were taken twice. The mean of the two readings was recorded as PW. The SphygmoCor system automatically calculated the augmentation index (Aix). The higher the Aix, the stiffer the artery (25).

Then, the distance between the carotid and femoral pulse sites was measured with a measuring tape. Subsequently, the distance was entered in a computer software programme for calculating blood flow velocity. Velocity is calculated as distance divided by time. The SphygmoCor probe was then placed at the two marking points to obtain the waveform, and measurements were taken twice. The mean of the measurements was recorded as PWV, with higher PWV values indicating stiffer arteries (25).

Statistical Analysis

Data were collected and recorded in case record form and analysed using the Statistical Package for the Social Sciences (SPSS) version 20. Demographic data were analysed using the Pearson chi-square test for categorical data and independent t-test for numerical data. Comparison of demographic data according to the severity of glaucoma was conducted using one-way analysis of variance (ANOVA) for numerical data with normal distribution. For numerical data with skewed distribution, the Kruskal-Wallis non-parametric test were used. The independent t-test was used to compare PWA and PWV between patients with POAG and controls. Multivariate analysis of covariance (ANCOVA) was used to study the potential effect of arterial stiffness on severity,

progression and risk factor for POAG with the presence of potential confounding factors, such as age, sex, BMI, BP, fasting blood glucose level, FLP, systemic hypertension, diabetes mellitus, hyperlipidaemia, and drugs (calcium channel blockers, beta blockers, angiotensin-converting enzyme inhibitors, oral hypoglycaemic agents, and statin). These confounding factors were detected based on multiple linear regression analysis. P values < 0.05 were considered statistically significant.

RESULTS

No significant differences in demographic data were found between the patients with glaucoma and the control subjects (Table I). The mean (±SD) dBP was significantly higher in the patients with glaucoma (81.7 ± 8.9 mmHg) than in the control subjects (78.3 ± 7.8 mmHg; Table I). However, no significant difference was observed in systolic BP (sBP). The mean BMI of the control subjects was higher than that of the patients with glaucoma, but the difference was not statistically significant (Table I). There was no significant difference of PWV (p = 0.838) and PWA (p = 0.789) between patients with POAG and control subjects in univariate and multivariate analysis (Table II).

Multiple linear regression was conducted to determine the potential confounding for PWV and PWA. There was significant linear relationship between age ([r^2= 0.12, 95%CI 0.03,0.21], p=0.010), sex ([r^2=-2.12, 95% CI -3.92, -0.32], p=0.022), sBP ([r^2=0.09, 95% CI 0.04,0.14], p=0.001) and diabetes mellitus (r^2= 3.89, 95% CI 2.05, 5.72], p=0.001) with PWV. While sex ([r^2=5.60, 95% CI 2.89, 8.32], p=0.001), sBP ([r^2= 0.14, 95% CI 0.06, 0.23], p=0.001), oral hypoglycaemic agent ([r^2= -3.34, 95% CI -6.09, -0.60], p=0.018) and BMI ([r^2= -0.34, 95% CI -0.66, -0.01], p=0.041) shown significant linear relationship with PWA. Based on these findings age, sex, sBP, diabetes mellitus, oral hypoglycaemic agent and BMI were included as confounding factors in the multivariate analysis.

On the basis of the AGIS scoring, 23 patients had mild, 18 had moderate, and 14 had severe glaucoma. Significant differences in the glaucoma parameters, namely mean deviation (MD), pattern standard deviation (PSD), and vertical cup-to-disc ratio, were found according to POAG severity (Table III). Systemic comorbidities, especially diabetes mellitus, was more prevalent in the mild severity group (Table III). We found no significant difference in PWA and PWV in relation to POAG severity (Table IV). The mean PWV was higher in the mild and moderate POAG groups than in the severe POAG group. The mean (±SD) PWA was highest in the severe POAG group (27.93 ± 5.77), but the differences between the groups were not statistically significant (p = 0.608).

Mean follow-up duration for patients with POAG was 4.7 ±3.1 years. A total of 10 eyes of patients with POAG fulfilled the criteria for progression of glaucoma after a mean follow-up duration of 5.8 ± 2.3 years. Patients without visual field progression have shorter duration of follow-up (4.4±3.2 years) compared to patients without progression of visual field but without statistically significant difference. The patients with progression of visual field had significantly higher PWV even after the confounding factors were controlled for (p = 0.036) (Table V).

Table I: Comparison of demographic data between POAG patients and controls

Variable	POAG N=55	Controls N=55	p value
Mean age , years (mean , ± SD)	66.9 ± 9.0 (40 – 82 y/o)	66.6 ± 8.9 (40 -82 y/o)	0.841*
Sex (n, %)			
Male	35 (63.6%)	35 (63.6%)	1.000#
Female	20 (36.4%)	20 (36.4%)	
Systemic disease			
Hypertension (n, %)	36 (65.5%)	35 (63.6%)	0.842#
Diabetes mellitus (n, %)	23 (41.8%)	26 (47.3%)	0.565#
Hyperlipidemia (n,%)	24 (43.6%)	31 (56.4%)	0.182#
Systemic medications			
CCB (n, %)	26 (47.3%)	20 (36.4%)	0.246#
BB (n, %)	10 (18.2%)	10 (18.2%)	1.000#
ACEi (n, %)	19 (34.5%)	16 (29.1%)	0.539#
OHA (n, %)	25 (45.5%)	18 (32.7%)	0.171#
Statin (n, %)	35 (63.6%)	31 (56.4%)	0.436#
	(Mean, SD)	(Mean, SD)	
sBP (mmHg)	144.82 (17.03)	138.53 (17.41)	0.058*
dBP (mmHg)	81.65 (8.87)	78.22 (7.84)	**0.034***
BMI, kg/m	24.91 (4.11)	26.28 (4.49)	0.099*
FBS (mmol/L)	7.09 (3.83)	7.38 (4.39)	0.717*
FLP (mmol/L)	5.24 (1.34)	5.23 (1.35)	0.968*

#p < 0.05 is considered statistical significance based on Pearson Chi- square test
*p < 0.05 is considered statistical significance based on Independent T test

CCB - calcium channel blocker
BB - beta blocker
ACEi - angiotensin converting enzyme inhibitors
OHA - oral hypoglycaemic agent

Table II Multivariate analysis on comparison of PWA and PWV between POAG patients and controls

Severity	Unadjusted (95% CI)	p value	Adjusted (95% CI)	F stat (df)	p value
PWA					
POAG	(25.44, 30.16)	0.333*	(25.21, 28.04)	0.112 (1)	0.739 **
Control	(25.73, 29.21)		(24.86, 27.68)		
PWV					
POAG	(13.25, 21.05)	0.234*	(14.58, 16.20)	0.042 (1)	0.838**
Control	(14.27, 16.55)		(14.71, 16.33)		

*p < 0.05 is considered statistical significance based on Independent T test
**p < 0.05 is considered statistical significance based on Multivariate ANCOVA

DISCUSSION

The blood circulatory system of the human body is composed of a complex network that originates from

Table III: Patient characteristics according to severity of POAG

Variable	Severity Mild n=23	Moderate n=18	Severe n=14	p value
Mean age, years (Mean ± SD)	64.9 ± 8.8	67.1 ± 10.8	69.9 ± 6.4	0.265[ш]
Sex (n,%)				
Male	15 (65.2%)	10 (55.6%)	10 (71.4%)	0.638[#]
Female	8 (34.8%)	8 (44.4%)	4 (28.6%)	
Systemic disease				
Hypertension (n,%)	17 (73.9%)	13 (72.2%)	6 (42.9%)	0.119[#]
Diabetes mellitus (n,%)	13 (56.5%)	9 (50.0%)	1 (7.1%)	**0.009**[#]
Hyperlipidemia (n,%)	14 (60.9%)	7 (38.9%)	3 (21.4%)	0.056[#]
sBP				
(Mean, SD)	144.83(14.78)	145.61(19.38)	143.79±18.49	0.957[ш]
(95%CI)	(138.44,151.21)	(135.97,155.25)	(133.11,154.46)	
dBP				
(Mean, SD)	82.35±8.45	79.17±9.58	83.71±8.51	0.321[ш]
(95%CI)	(78.70,86.00)	(74.40,83.93)	(78.80,88.63)	
BMI				
(Mean, SD)	24.59(4.30)	26.07(4.21)	23.96(3.58)	0.319[ш]
(95%CI)	(22.73,26.45)	(23.97,28.17)	(21.89,26.02)	
FLP				
(Mean, SD)	5.02(1.27)	5.67(1.08)	5.02(1.68)	0.248[ш]
(95%CI)	(4.48,5.58)	(5.14,6.20)	(4.04,5.99)	
FBS				
(Median,IQR)	6.80(6.50)	6.30(2.18)	5.20(0.95)	0.056[ш]
(95%CI)	(6.36,10.55)	(5.58,8.41)	(4.06,5.91)	
Ocular Parameters CCT, um				
(Mean,SD)	512(18)	513(32)	510(13)	0.933[ш]
(95%CI)	(505.0, 520)	(497.5, 529.8)	(503.1, 518.3)	
MD, dB				
(Mean,SD)	-4.42(2.39)	-10.84(3.07)	-24.94(5.39)	**<0.001**[ш]
(95%CI)	(-5.46, -3.40)	(-12.37, -9.31)	(-28.06,-21.83)	
PSD, dB				
(Mean,SD)	5.20(2.82)	8.08(2.67)	8.71(3.24)	**<0.001**[ш]
(95%CI)	(3.98, 6.42)	(6.75, 9.41)	(6.84, 10.58)	
IOP, mmHg				
(Median±IQR)	14.0(4.0)	14.0(4.0)	15.0(6.0)	0.180[##]
(95%CI)	(13.8, 16.5)	(13.2, 16.5)	(14.7, 19.0)	
VCDR				
(Median±IQR)	0.80(0.10)	0.80(0.20)	0.90(0.11)	**0.003**[##]
(95%CI)	(0.73, 0.79)	(0.74, 0.83)	(0.82, 0.92)	

[ш]p < 0.05 is considered statistical significance based on One-way ANOVA
[#]p < 0.05 is considered statistical significance based on Pearson Chi- square test
[##]p < 0.05 is considered statistical significance based on Kruskal Wallis test

Table IV: Multivariate analysis of PWA and PWV on severity of glaucoma

Severity	Adjusted (95% CI)	F stat (df)	p value
PWA			
Mild	(24.99, 29.53)		
Moderate	(24.36, 29.36)	0.049 (2)	0.953**
Severe	(23.63, 29.73)		
PWV			
Mild	(13.98, 16.94)		
Moderate	(14.24, 17.50)	0.100 (2)	0.905**
Severe	(14.00, 17.97)		

**p < 0.05 is considered statistical significance based on Multivariate ANCOVA

the heart. To reach the eye, which is one of the end organs, the blood vessels change in morphology and size (26). Nevertheless, the ocular and systemic circulations remain connected. Any change in the systemic circulation is assumed to affect the ocular

Table V: Multivariate analysis of PWA and PWV in visual field progression of POAG patients

	Adjusted (95% CI)	F stat (df)	p value
PWA			
Progress (10)	(21.71,28.06)	2.101(1)	0.155**
Non-progress (45)	(26.06,28.84)		
PWV			
Progress (10)	(15.71, 19.73)	4.745 (1)	**0.036****
Non progress (45)	(14.41, 16.17)		

**p < 0.05 is considered statistical significance based on Multivariate ANCOVA
Confounding factors controlled are age, sex, BMI, sBP, dBP, FBS, FLP, HPT, DM, HPL, CCB, BB, ACEi, OHA and statin.

circulation directly or indirectly (27). In this study, the arterial stiffness of large and medium-sized arteries using SphygmoCor was postulated to indirectly represent the changes of the vessels at the optic nerve head (ONH). We used applanation tonometry based SphygmoCor, which is accurate and reliable with a huge database on healthy population and patients with diseases (30). However, this technique requires trained operator and difficult to conduct in obese patients (31). Currently, there is cuff based SphygmoCor available in the market, which less operator dependent and not affected by body size but less accurate compared to tonometry based (30,31).

Age plays a significant role in arterial stiffness and risk of POAG (28). The result of the multiple linear regression analysis in the present study indicates that age affects arterial stiffness. Hence, the recruitment of age-matched control subjects is obviously important to minimise age-related bias. Women are predisposed to arterial stiffness more than men (29), whereas men are found to be slightly more at risk of developing POAG (30). Hence, the control subjects were also sex matched to the patients with POAG.

Systemic comorbidities such as systemic hypertension and diabetes mellitus are also known to affect arterial stiffness and are identified as the risk factors of POAG (5,26). However, the relationships of these diseases with glaucoma remain controversial as to whether they are direct or co-existing risk factors that are part of the aging process. In addition, arterial stiffness was affected by sBP in our study. Ideally, patient with systemic hypertension and diabetes mellitus should be excluded from the study, as the result may influence the arterial stiffness measurement. In this study, however, we did not exclude patients with systemic comorbidities, as this is impossible and impractical. As POAG is a disease of longevity, systemic comorbidities in patients with advanced ages are almost impossible to exclude. However, after controlling for these major confounding factors, we still found no significant association between arterial stiffness and POAG in the Malay patients. Similar findings were reported in various other populations (17,20,31). It is therefore likely that arterial stiffness is

not a risk factor for the development of POAG.

The question remains on whether arterial stiffness accelerates the progress of optic neuropathy in POAG. Arterial stiffness was found to affect the severity of chronic kidney disease (32). Both the kidney and eye are end organs; thus, a similar effect can potentially be observed. Pre-existing retinal ganglion cell damage in POAG may progress faster when perfusion to the ONH is inadequate owing to arterial stiffness and lead to a more severe disease (20). However, we found no significant differences in PWV and PWA in relation to POAG severity in the present study. So far, no study has analysed the correlation between arterial stiffness and glaucoma severity; thus, further comparison is not possible. Our finding is perhaps affected by the unequal numbers of patients according to POAG severity, which caused the skewness of the data distribution. Sample size calculation in the present study should be based on the difference of PWV and PWA according to severity of POAG rather than between controls and patients with POAG. This cause major weakness in this study. Nevertheless, no association may truly exist between arterial stiffness and glaucoma severity. SphygmoCor measurements of aortic stiffness may not represent the micro-ocular circulation.

We found a significant difference in PWV between the progressing and non-progressing cases. PWV is a direct measure of large arterial stiffness and is measured at the central carotid and femoral sites. On the other hand, PWA is a proxy measurement of arterial stiffness that is measured at the peripheral radial artery. It may be affected by ventricular ejection, peripheral haemodynamic, and the properties of the large arteries (33). Graham et al found a similar association in their study that involved 126 patients with glaucoma and 66 control subjects (17). There is also a possibility of carotid stenosis in these patients (38). Unfortunately, we did not include any investigation to rule out carotid stenosis in this study. In addition, the present study, only ten patients conformed to the criteria for visual field progression, which may not truly represent the potential role of arterial stiffness in the progression of POAG.

In this study, we assumed that IOP and IOP fluctuation play a minimal role in the progression of POAG. We assumed that all the patients with POAG achieved good IOP control on the basis of their IOP readings < 18 mmHg throughout the follow-up period. The target pressure was not individualised according to POAG severity. The potential effect of diurnal variation and long-term IOP fluctuation was not included (39). The progression of POAG is probably multifactorial, that is, a combination of the mechanical effects of uncontrolled IOP and impairment of blood supply to the ONH.

A longitudinal study is best for elucidating the changes in arterial stiffness in chronic diseases such as POAG. A 9-year longitudinal study that involved 3274 middle-aged Japanese men showed that inflammation associated with progressive arterial stiffness led to gradual BP increase (40). Arterial stiffness also gradually aggravated chronic kidney disease in a longitudinal study (41). A cross-sectional study may not well capture the changes in arterial stiffness in patients with POAG, especially with the strong influences of age and the chronicity of the disease.

Arterial stiffness may play an indirect role in retinal microcirculation (42,43). The retinal vasculature is comprised of end arteries, which are lined by the endothelium. The endothelial layer in the systemic vasculature is also affected by arterial stiffness (44). No evidence suggests that similar changes occur in the retinal circulation. Postulating that the stiffness of medium and large arteries reflects the retinal perfusion may not justify the potential association. However, some other factors that affect the ocular blood flow in glaucoma are worth considering, including increased local resistance to flow, elevated blood viscosity, and reduced ocular perfusion pressure (45). Autoregulation is a protective mechanism in the retinal circulation. This mechanism might have remained intact in the patients recruited in this study and stabilised the perfusion to the ONH. These factors were not quantified in the present study.

Arterial stiffness is known as one of the signs of vascular aging. Aging systemic vessels are not associated with aging eyes or POAG in the present study. Other factors that may exert stronger effects on perfusion to the ONH should be elucidated, as identification of these factors is important to inhibit further damage secondary to POAG.

CONCLUSION

In this cross-sectional study, the arterial stiffness of medium and large arteries showed no association with the severity and progression of POAG in the Malay patients. Further longitudinal study with multiple measurements of arterial stiffness over a period in a larger cohort of patients is recommended.

ACKNOWLEDGEMENTS

This study was partially funded by the Universiti Sains Malaysia Research University Individual Grant 1001/PPSP/812101. We thank all the staff in the eye clinic of Hospital Universiti Sains Malaysia and the patients who participated in this study.

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