THE EFFECT OF ARTERIAL STIFFNESS ON THE SEVERITY AND PROGRESSION OF PRIMARY OPEN ANGLE GLAUCOMA IN MALAY PATIENTS

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Abstract

Introduction

The pathogenesis of glaucoma is still unclear. The direct effect of elevated intraocular pressure (IOP) has been proposed as important risk factor for developing of glaucomatous optic neuropathy (GON) based on mechanical theory. Despite well controlled IOP, glaucoma still progress in some patients. Vascular theory suggested that insufficient blood supply causes GON. A combination of high IOP and inadequate ocular perfusion may theoretically accelerate GON lead to rapid progression and more severe disease.

Objectives

Our objectives are to compare the mean of arterial stiffness between POAG patients and controls and to compare the mean of arterial stiffness on severity and progression of POAG.

Methodology

110 Malay patients were recruited for this study. 55 patients were POAG while 55 were age and gender matched controls. Arterial stiffness was measured in pulse wave analysis (PWA) and pulse wave velocity (PWV) parameters using sphygmocor device.

Results

Mean age was 66.9 ± 9.0 years in POAG group and 66.6 ± 8.9 years in controls. PWA was 26.98 ± 6.15% in POAG and 25.90 ± 5.39% in controls while PWV was 15.73 ± 4.14 m/s in POAG and 15.18 ± 3.26 m/s in controls. There were no significant differences of PWA and

PWV between the two groups. Meanwhile, no significant difference of PWA and PWV on the severity and progression of POAG were noted. However, PWV showed significant difference on progression of POAG after analysed with multivariate ANCOVA with $p < 0.05$.

Conclusion

In this study, there were no significant difference of arterial stiffness between POAG and controls and the severity of POAG. PWV was found to be significant on progression of glaucoma after controlling the confounding factors.

ABSTRAK

Introduction

Patogenesis glaukoma masih kurang jelas. Berdasarkan kepada teori mekanikal, Kenaikan tekanan bola mata adalah satu faktor secara langsung menyebabkan glaukomatous saraf mata. Walaupun tekanan bola mata telah dikawal, glaukoma masih didapati berkembang di kalangan pesakit. Teori saluran darah mencadangkan kekurangan peruntukan darah menyebabkan glaukomatous saraf mata. Kombinasi tekanan mata tinggi dan kekurangan perfusi mata dijangka mempercepatkan keterukan dan perkembangan glaukoma.

Objektif

Objektif kami adalah membandingkan purata keanjalan saluran arteri antara pesakit glaukoma sudut terbuka dengan kumpulan kawalan dan juga dari segi keterukan dan perkembangan antara pesakit glaukoma sudut terbuka.

Tatacara

Seramai seratus sepuluh pesakit telah menyertai kajian ini. Lima puluh lima pesakit glaukoma yang dipilih telah diseratakan umur dan jantina dengan kumpulan kawalan. Semua pesakit telah menjalani pengukuran keanjalan arteri iaitu gelombang nadi dan kelajuan nadi dengan memakai alat Sphygmocor.

Keputusan

Purata umur pesakit glaukoma adalah 66.9 ± 8.0 tahun manakala 66.6 ± 8.9 tahun bagi kumpulan kawalan. Purata analisa gelombang nadi adalah 26.98 ± 6.15 % bagi pesakit glaukoma dan 25.90 ± 5.39 % bagi kumpulan kawalan (p=0.333). Purata kelajuan gelombang nadi adalah 15.73 ± 4.14 m/s bagi pesakit glaukoma dan 15.18 ± 3.26 m/s bagi kumpulan kawalan (p=0.443). Keputusan ini menunjukkan tiada perbezaan keanjalan arteri antara pesakit glaukoma dan kumpulan kawalan. Selain daripada itu, tiada perbezaan yang jelas didapati dari segi keterukan (p=0.608, p=0.344) dan perkembangan glaukoma (p=0.218, p=0.234). Walaubagaimanapun, kelajuan nadi didapati ada berkaitan dengan perkembangan glaukoma selepas dianalisasi oleh multivariate ANCOVA (p=0.036).

Kesimpulan

Kajian ini mendapati tiada perbezaan keanjalan arteri antara pesakit glaukoma dengan kumpulan kawalan. Di samping itu, kajian ini juga tidak mendapati perbezaan dari segi keterukan penyakit glaukoma dan pekembangannya. Namun demikian, kelajuan nadi menunjukkan perbezaan dengan perkembangan glaukoma selepas faktor mengeliru dikawal.

Kata Kunci – glaukoma sudut terbuka, keanjalan arteri, analisa gelombang nadi, kelajuan gelombang nadi

INTRODUCTION

1.1 Glaucoma

1.1.1 Definition of glaucoma

Glaucoma is a chronic degenerative optic neuropathy characterised by its specific appearance of optic nerve damage and visual field defect. The morphologic changes of optic nerve includes cupping and pale optic disc which is due to loss of retinal ganglion cells (Quigley and Green, 1979). It is one of the leading causes of irreversible blindness worldwide.

Glaucoma can be divided into two major categories according to the angle structure: open angle and angle closure glaucoma. Open angle glaucoma is often associated with increased intraocular pressure (IOP), however in certain population, the IOP can be within normal limits, so called normal tension glaucoma (NTG).

1.1.2 POAG

Of the many types of glaucoma, primary open angle glaucoma (POAG) is the most common form of glaucoma (Quigley and Broman, 2006). POAG can occur with or without elevation of intraocular pressure (IOP). Open angle with elevation of IOP is called high tension glaucoma (HTG) whereas open angle without elevation of IOP is termed NTG (Foster *et al.*, 2002). However, in many literatures both NTG and HTG are considered under the same category of POAG (Lewis *et al.*, 1983; Miller and Quigley, 1987; Motolko *et al.*, 1982; Yu *et al.*,

1997). Elevated IOP is an important risk factor and remain the only modifiable risk factor for POAG (Le *et al.*, 2003). The presence of positive family history of glaucoma is another risk factor (Wolfs *et al.*, 1998).

Glaucoma is a complex disease. There is no single standardised criteria for diagnosing glaucoma especially POAG. There are wide variation in between optic disc size and IOP in between populations. This should be taken into account when evaluating the optic disc for different ethnics. African is known to have largest cup disc ratio with intermediate in Asians and smallest in whites. (Tsai *et al.*, 1995). The variation not only exist in different ethnic groups but within the same ethnics as well. Study showed that greater vertical cup-to-disc ratio (VCDR) is related to male sex, higher IOP and lower body mass index (BMI) in normal Malay population. (Amerasinghe *et al.*, 2008)

Thus, the relation in between CDR and visual field defect is complex and it is hard to standardise the measurements for each and every individual. Glaucoma cases can be classified according to three levels of evidence (Foster *et al.*, 2002). First, the highest level of certainty requires optic disc abnormalities (VCDR > 97.5^{th} percentile in the normal population) and visual field defect compatible with glaucoma. Second, if a visual field test could not be performed satisfactory, a severely damaged optic disc (VCDR > 99.5^{th} percentile of the normal population) would be sufficient to make the diagnosis. Lastly, if the optic disc could not be examined because of media opacity (no field test was possible), an IOP exceeding the 99.5^{th} percentile of the normal population, or evidence of previous glaucoma filtering surgery , may be taken as sufficient for a diagnosis of glaucoma.

Characteristics of glaucomatous field defects include symmetrical defect across the horizontal midline, located in the mid periphery, clustered in neighbouring test points, reproducible on at least two occasions, not explained by any other disease and with reliable indices. Apart from that, the glaucoma hemifield test (GHT) should be graded "outside normal limits" with a cluster of three contiguous points at the 5% level on the pattern deviation plot, using 24-2 test pattern of Zeiss Humphrey field analyser (Foster *et al.*, 2002).

The diagnosis of POAG is thus, based on these findings, depends on the existence of optic nerve damage characterised by specific characteristic of optic nerve changes and visual field defect. The status of IOP as defining characteristic of glaucoma has evolved over times. Previously, IOP of 21mmHg has been used as cut off point for definition (Ritch *et al.*, 1996).

The existence of NTG as separate disease is disputed by many (Iester and Mikelberg, 1999; Miller and Quigley, 1987; Motolko *et al.*, 1982). Nonetheless, there is presence of evidence that reducing IOP in NTG patients can modify the nature of disease progression (Wilson, 1997; Zhao *et al.*, 1998). In some NTG patients, despite lowering of the IOP, they continue to experience progressive visual field loss leading to irreversible loss of vision (CNTGS, 1998). Some patients with higher than normal IOP remain stable with small visual field deterioration (Kass *et al.*, 2002). This implies that mechanical theory eg IOP is not the sole cause of glaucomatous neuropathy.

NTG as a subtype of POAG was found to have a median IOP of 20mmHg or less in 10 baseline measurement (CNTGS, 1998). To establish the diagnosis of NTG, one has to rule out other types of glaucoma and optic neuropathy. Clinical assessment with systemic comorbids and brain imaging is recommended in non glaucomatous optic neuropathy such as compressive optic neuropathy, ischemic optic neuropathy and etc (Kamal and Hitchings, 1998).

1.1.2 Epidemiology of POAG

The prevalence of visual impairment and blindness were estimated by World Health Organisation (WHO) to be 285 million visually impaired and 39 million blind in 2010 (Pascolini and Mariotti, 2011). The most common visual impairment is uncorrected refractive error (43%) followed by cataract (33%) and glaucoma (2%). The most common causes of blindness is cataract (51%) followed by glaucoma (8%) .

Several studies have been conducted regarding the prevalence of glaucoma with different ethnic groups and geographic distribution (Klein *et al.*, 1992; Mitchell *et al.*, 1996). In Beaver Dam Eye Study, the overall prevalence of definite open-angle glaucoma was 2.1% with cases increased with age from 0.9% in people 43 to 54 years of age to 4.7% in people 75 years of age or older (Klein *et al.*, 1992). In Australia, The Blue Mountains Eye Study showed prevalence of POAG and OHT of 3.0% and 3.7% respectively (Mitchell *et al.*, 1996).

The Rotterdam Eye Study showed prevalence of POAG was 0.8% and men were double than women (Wolfs *et al.*, 2000). The prevalence of glaucoma was 3.6% in Beijing Eye Study with POAG (2.6%) and PACG (1.0%) (Wang *et al.*, 2010) .

The Egna Neumarkt Study showed prevalence of glaucoma in Italy with high tension glaucoma (2.0%), OHT (2.1%) and PACG (0.6%) (Bonomi *et al.*, 1998). However, prevalence of glaucoma in Japan was POAG (2.62%), OHT (1.37%) and PACG (0.34%) (Shiose *et al.*, 1990).

Rotterdam study seems to have to lowest prevalence of 0.8% , most probably due to recruitment of patients of only 55 years and above compare to most studies which includes 40 years and above.

It is estimated that the number of glaucoma patients will be increased from 60.5 million in 2010 to 79.6 million in 2020 (Quigley and Broman, 2006). South East Asia is estimated to have increment of 2.89% of glaucoma population with 3.81% of POAG and 3.72% of PACG world population by 2020.(Quigley and Broman, 2006) The prevalence of glaucoma among Malay population in Singapore were 3.4% of study population with POAG (2.5%), PACG (0.12%) and others (0.61%).(Shen *et al.*, 2008).

In Malaysia, National Eye Survey also showed that glaucoma is the fifth leading causes of blindness in 1996 (Zainal *et al.*, 2002). In this study, the leading cause of blindness was cataract (39%) and uncorrected refractive error (48%) was the major cause of visual impairment. However, this study was conducted relied

solely on visual acuity, without biomicroscopy examination which may underestimate the prevalence of glaucoma. Clinic based study in urban population in Malaysia reported that glaucoma was the second most common eye disease in the eye clinic (SC Reddy, 2008) . The most common eye disease in this study was cataract (32.9%), followed by glaucoma (23.4%), refractive errors (10.8%) and diabetic retinopathy (9.7%).

The incidence of glaucoma is expected to rise with the growth of elderly population. The disease is important to be diagnosed earlier for early therapy, not only to delay the progression but to reduce the cost of treatment as well. In the USA, glaucoma costs health care system an estimate of $2.5 billion annually which $1.9 billion represent direct cost and $0.6 billion represent indirect cost. The total annual direct cost of glaucoma treatment per patient can range from $523 in the early stage of glaucoma to $2125 in the advanced stage of glaucoma with mean of $1483 per patient.(Sponsel *et al.*, 1995) This showed that the more severe the disease the higher the cost.

However, the scope of the problem probably bigger than what we expected as there are still large proportion of individuals remains undiagnosed or inadequately treated (McKean-Cowdin *et al.*, 2008).

1.1.3 Pathophysiology

Under normal physiologic condition, as IOP increases, arterioles dilate to decreased vascular resistance in response to a decrease in pulse pressure, thus

maintaining a constant oxygen tension at the optic nerve. In healthy subjects, autoregulation has been shown to maintain constant ocular blood flow over a wide range of perfusion pressure (Liu *et al.*, 2003). Evidence showed that blood flow in both retina and optic nerve head was autoregulated by neural, endothelial and myogenic mechanism (Flammer and Mozaffarieh, 2008). Ocular blood flow had been shown to remain constant when the perfusion pressure was altered by intraocular pressure or systemic blood pressure (Schmetterer *et al.*, 1997).

Evidence suggest that subjects with glaucoma fail to adapt to changes in either IOP or blood pressure that cause fluctuations in perfusion pressure, ultimately resulting in unstable blood flow to the retina and optic nerve head (Harris *et al.*, 2001). In recent years, alterations in ocular blood flow and abnormal vascular autoregulation are emerging key components of the disease process in glaucoma. Compromised ocular blood flow and deranged vascular autoregulation in the optic nerve head could be as important as intraocular pressure (Flammer and Mozaffarieh, 2008; Hayreh, 2001).

Various systemic and local factors can cause low perfusion pressure and breakdown of autoregulatory mechanism such as aging, hypertension, diabetes, hyperlipidemia, arteriosclerosis, atherosclerosis (Hayreh, 1995; Langham *et al.*, 1991; Werner *et al.*, 2001).This results in unstable ocular perfusion and further ischemic and reperfusion damage.

Three components have been related to ocular blood flow reduction in glaucoma which are increased local resistance to flow, decreased ocular perfusion pressure and increased blood viscosity (Shaarawy *et al.*, 2009).

Local resistance to ocular blood flow can be due to either structural changes or functional changes. Structural changes such as anatomic variations in the vessels, obstruction of the lumen by thrombosis or arteriosclerosis and spasm whereas functional changes can be defective autoregulation of blood flow (Flammer *et al.*, 1999; Sharrett *et al.*, 1999). Increased vascular stiffness can increase the resistance which may contribute to impaired autoregulation in certain glaucoma patients. Arterial stiffness can be affected by several factors such as age, hypertension, diabetes mellitus, hyperlipidemia and atherosclerosis (Blacher *et al.*, 1999; Brouwers *et al.*, 2009; Ogawa *et al.*, 2005; Tomiyama *et al.*, 2003; van Popele *et al.*, 2001).

Clinical trials had demonstrated inadequate blood flow in patients with POAG in retinal, choroidal and retrobulbar circulation (Butt *et al.*, 1995; Chung *et al.*, 1999b; Yin *et al.*, 1997). Abnormalities in ocular perfusion pressure, nocturnal hypotension, aging of vasculature, optic disc hemorrhage and migraine had been reported to be associated with POAG (Bonomi *et al.*, 2000; Drance *et al.*, 2001; Hayreh *et al.*, 1994; Leighton and Phillips, 1972).

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Siasos et al (2011) found out arterial stiffness is associated with POAG (Siasos *et al.*, 2011). On the other hand, few studies shown no significant findings between arterial stiffness and POAG (Chiba *et al.*, 2008; Graham *et al.*, 2013). Therefore, arterial stiffness and POAG issue is still controversial and most studies are conducted in western countries. Therefore, a study of arterial stiffness on POAG in Malay patients could be beneficial to Malaysia as Malay represent one of the largest ethnic group in Southeast Asia.

1.1.4 Progression of POAG

1.1.4.1 Natural course of POAG

The rate of progression in glaucoma patients receiving treatment was estimated at approximately 3% per year (Smith, 1985). However, this rate starts at the residual visual field of 70%. Study has also reported that POAG progression in untreated person from early to end stage had an average of 14.4 years if the IOP is in between 21-25 mmHg (Jay and Murdoch, 1993). The progression rate can be as long as 38 years if the disease is optimally treated with surgical intervention. The rate of progression varies individually with some eyes show curvilinear loss and some linear loss.

Monitoring progression of glaucoma is a challenge for clinician. After glaucoma is diagnosed, serial IOP, cup to disc ratio (CDR), retinal nerve fibre layer (RNFL)

and visual field measurements will be conducted to monitor the progression. In some patients, progression can still be seen despite well controlled IOP. This could be due to other factors such as vascular factors causing progression of glaucoma (Schmidl *et al.*, 2011).

Morphological changes suggestive of progression can be evaluated with serial stereophotography of optic disc and optical coherence tomography (OCT) to assess any increase excavation of the neural rim with increase cup disc ratio, notching, rim thinning, disc hemorrhage and thinning of retinal nerve fibre layer.

For functional changes, automated perimetry is used for visual field monitoring. Small sensitivity deficits in paracentral regions may initially extend and deepen, becoming arcuate in appearance and nasal step type defects may enlarge temporally (Mikelberg and Drance, 1984). Later, the defects will join with the physiological blind spot and widen. Worsened visual acuity is also used as a sign of progression in end stage patients with diffuse depressed visual field (Membrey *et al.*, 2000).

VF measures are not perfectly repeatable in normal individuals and can exhibit both short and long term variations (Spry and Johnson, 2002). This is even more obvious and greatly increased in glaucoma. It is a complex task to distinguish progressive glaucomatous visual field loss from test variability.

The procedures used for detection of glaucomatous visual field progression can be grouped into four categories : 1) Clinical judgement, which consists of simple

subjective observation of sequential visual field test results (Heijl *et al.*, 1990); 2) visual field defect classification systems, whereby specific criteria are used to stratify field loss by discrete score and define progression as score change over time, such as the CIGTS Scoring System (Musch *et al.*, 1999) ; 3) trend analysis, which follow test parameters sequentially over time to determine the magnitude and significance of patterns within the data, for example linear regression (HOLMIN and Krakau, 1982); and 4) event analysis, which identify single events of significant change relative to a reference examination (Fankhauser and Jenni, 1981).

The natural course of NTG is variable, with some cases progress slowly without any treatment but others progress rapidly (Anderson and Drance, 2001). Collaborative Normal Tension Glaucoma Study Group (CNTGS) reported that lowering IOP by 30% showed a slower rate of visual field progression (Zhao *et al.*, 1998). However, progression of the visual field damage continues in 20% of NTG patients even though IOP has been lowered 30% or more from the baseline (Zhao *et al.*, 1998).

Long term IOP fluctuation is associated with VF progression in patients with low mean IOP (Caprioli and Coleman, 2008). This could be due to greater IOP fluctuation in low mean IOP patients with further stress imposed on the nerve tissue and damages occurs. Vascular theory might be the contributing factor, though the IOP is controlled but disease still progress.

1.1.4.2 Definition of Progression

There are few examples of definitions of visual field progression from multicenter clinical trials such as AGIS, EMGT and CIGTS.

Early Manifest Glaucoma Trial Group (EMGT) studied on early glaucoma with mean deviation of -4 dB and median IOP of 20mmHg (Heijl *et al.*, 2002). Visual field progression was defined as the same 3 or more test point locations showing significant deterioration from baseline on glaucoma change probability maps (GCPMs). Optic disc progression was determined by 2 masked graders using flicker chronoscopy plus side by side comparison by a third grader to decide if definite optic disc progression was present. Study revealed that by reducing IOP of 25% or more, the glaucoma progression was less frequent. (Heijl *et al.*, 2002).

Collaborative Initial Glaucoma Treatment Study (CIGTS) was done on newly diagnosed POAG patients with medically treated versus surgically treated group (Musch *et al.*, 1999). The CIGTS scoring was based on Statpac Total Deviation Probability Maps rather than on decibel deviations. As with AGIS, only clustered depressed points counted, and the field score depended on the significance level of depression at each test location and its neighbours. The CIGTS final score ranged from 0 to 20. Progression required a worsening of MD by 3 or more dB compared with that at baseline. Study showed that patients who had advanced visual field damage and treated surgically had less visual field progression than those who treated medically (Musch *et al.*, 2009).

AGIS study was carried out on patients with advanced glaucoma and aimed to look at the outcome of trabeculoplasty and trabeculectomy in these patients (Gaasterland *et al.*, 2000). AGIS VF scoring was based on the number and depth of depressions from age related normal threshold value displayed in the Statpac Total Deviation maps of the Humphrey perimeter (Carl Zeiss Meditec, Dublin CA). The scores ranged from 0 (normal) to 20 (worst field status). Reductions of sensitivity must have met certain minimum criteria to be considered: for example, hemifield defects must have consisted of at least 3 clustered test point locations with depressed sensitivity in the same superior or inferior hemifield. The maximum field score was 9 in each hemifield plus 2 in the nasal area. The glaucoma progression was defined as worsening of the score by at least 4 units, compared to the baseline reference field in 3 consecutive tests. Study showed that patients with IOP consistently below 18 mmHg was almost no visual field loss.

Comparison had been done on the various methods of scoring system namely AGIS, CIGTS and EMGT. Joanne Katz et al (1999) reported that the detection rate of progression using AGIS, CIGTS and EMGT scoring was 11%, 22% and 23% respectively (Joanne Katz, 1999). In addition, clinical assessment of progression is almost identical to EMGT scoring. In this study, it was found agreement between clinician was better than scoring methods (Joanne Katz, 1999). However, Werner and colleague (1988) reported that scoring method was better than clinician agreement (Werner *et al.*, 1988). Therefore, it is still difficult to determine which of analytical methods is the best in classifying glaucoma progression. Visual fields that appear progress over time may improve at subsequent visits. Separating true progression from visual field fluctuations is not

an easy task due to patients learning effects, fatigue and physiological state of the eye (Medeiros and Alencar, 2010).

As a general rule, visual field should not be using as stand alone test to monitor progression. Xin et al (2011) reported that calculating progression showed poor agreement if only visual field or stereophotograph alone was used. Thus, combination of functional and structural test when determining progression is recommended (Xin *et al.*, 2011).

1.1.4.3 Factors affecting progression in POAG

Prognostic factors for glaucoma progression have been studied in large multi centre randomised clinical trials.

Age has been shown as progression risk factor in several studies include EMGT and AGIS study (De Moraes *et al.*, 2011; Gordon *et al.*, 2002; Leske *et al.*, 2007; Musch *et al.*, 2009; Nouri-Mahdavi *et al.*, 2004).

Apart from age, baseline high IOP and IOP fluctuation are also an important risk factor (Gordon *et al.*, 2002; Leske *et al.*, 2007; Nakagami *et al.*, 2006; Nouri-Mahdavi *et al.*, 2004).

Elevated IOP during follow up was a strong factor for glaucoma progression with the hazard ratio increasing by 11% for every 1 mmHg of higher IOP in EMGT study (Bengtsson *et al.*, 2007). IOP dependent parameters such as mean IOP

follow up, peak IOP and IOP fluctuation were also noted to be associated with increased risk of progression (De Moraes *et al.*, 2011). Patients with higher mean IOP follow up tends to have higher peak IOP.

In EMGT study, disc hemorrhage and thinner CCT are also significant glaucoma progression factors (Leske *et al.*, 2007). On the other hand, longer follow up and higher number of glaucoma interventions are associated with visual field progression in AGIS study (Nouri-Mahdavi *et al.*, 2004). In addition, increase nerve fibre layer thinning, concurrent glaucoma therapy, CDR asymmetry and disc crescent play a role in the progression of OHT to POAG (Quigley *et al.*, 1994).

Female gender, migraine and disc hemorrhage have also reported to be the risk factors associated with progression in NTG (De Moraes *et al.*, 2011; Drance *et al.*, 2001). Variable rate of deterioration, as well as lack of progression in a substantial number suggest IOP might not be the only contributing factor. Vascular factors might play a role in glaucoma progression.

1.2 Macrovascular Arterial stiffness

1.2.1 Mechanism of arterial stiffness

The pathogenesis of glaucoma is still unclear today. Both mechanical and vascular theory has been proposed (Fechtner and Weinreb, 1994). The mechanical theory suggests that elevated IOP is important risk factor for developing of glaucomatous optic neuropathy. Increased IOP causes stretching of the laminar beams which leads to bowing of lamina cribosa and damage the retinal ganglion cells (Emery *et al.*, 1973). The vascular theory postulates glaucomatous optic neuropathy was due to insufficient blood supply caused by vascular dysregulation leading to unstable ocular perfusion, causing further ischemia and reperfusion damage. (Flammer *et al.*, 2002).

Various mechanism of vascular regulatory dysfunctions have been proposed such as atherosclerosis, vasospasm, and endothelial dysfunction that could contributes to reduced ocular blood flow (Moore *et al.*, 2008). Vascular dysregulation can be caused by loss of ability of autoregulation of blood to maintain ocular blood flow with adequate oacular perfusion despite changes in local vascular parameters (Flammer and Mozaffarieh, 2008).

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Arterial stiffness was described as reduced capability of an artery to expand and contract in response to pressure changes (Bramwell and Hill, 1922). Elasticity of the arteries are important to smoothen flow from intermittent ventricular ejection to more steady flow within the peripheral tissues. During systole, the artery which contains high elastin fibre allows distension whereas during diastole, the blood is pushed forward through the arterial tree due to its elastic recoil properties. More distal arteries have lesser elastic fibres that makes them less distensible (Roach and Burton, 1957). The increase of arterial stiffness that occurs with age is largely due to degeneration of the elastic fibres (Avolio *et al.*, 1998). There is a possibility that a combination of mechanical and vascular accelerate the disease progression (Chung *et al.*, 1999a).

In healthy and compliant arteries, the pressure wave from left ventricles travels through the arterial trees and reflected at multiple peripheral sites. As a result, the arterial pressure waveform at any site is a combination of forward travelling waveform and backward reflection waveform. The two waveforms merge during diastole and augment coronary perfusion. As the arterial wall thickens and stiffer with aging, the pressure waves travel faster and reflected pressure wave returns during the systolic phase, increasing the systolic pressure and thus increasing left ventricular load (Nichols *et al.*, 2011). Arterial stiffness can lead to a fall in diastolic pressure resulting in widened pulse pressure which can cause organ impairment due to greater pressure fluctuation (O'Rourke and Safar, 2005). Arterial stiffness is increased by three mechanism, namely 1) the breakdown of

the elastic structure, 2) damage to the endothelium or smooth muscle and 3) increase in mean arterial pressure.

1.2.2 Various methods of arterial stiffness measurements

Commonly measured indices of arterial stiffness include compliance, distensibility, elastic modulus, pulse wave velocity, stiffness index and augmentation index (AIx) (Oliver and Webb, 2003). There are few non invasive methods of assessing arterial stiffness namely sphygmocor, arterial ultrasonography, magnetic resonance imaging (MRI), carotid augmentation index (AIx) and digital pulse contour analysis (DPCA). They can be compared in terms of ease of use, quality of validation, affordability, freedom from operator bias, evidence of prognostic value and endothelial function testing. PWV is deemed to have highest prognostic value among all (Laurent *et al.*, 2006; Oliver and Webb, 2003).

1.2.3 Arterial stiffness measurement device (Sphygmocor)

Sphygmocor is a simple to use, non invasive and accurate device for arterial stiffness measurement . The principle of applanation tonometry is used to obtain a high fidelity signal without penetrating the skin or blood vessels (Siebenhofer *et al.*, 1999). Sphygmocor system consists of desktop PC, electronic module, tonometer probe and footswitch. In this system, the peripheral arteries mainly the

carotid, femoral or radial artery is flattened between the probe and the underlying structure. The intra arterial pressure pulse is then transmitted through the wall of the artery and the underlying tissue to the sensor in the tonometer and the result is generated by the computer (Sandy *et al.*, 2006).

The velocity of the blood pressure pulse waveform is dependent on the stiffness of the artery along which the pulse is travelling. It is the speed of the pressure wave travelling along an arterial segment. The higher the velocity, the more stiffness the artery is (Mackenzie *et al.*, 2002)

The device is available in portable form, therefore, useful in both hospital and clinic settings. Results of reproducibility will depend on both the stability of the subject's physiological status and operator skill (Sandy *et al.*, 2006). Although there are numbers of methods and devices to measure arterial stiffness either systemic, regional or locally, Sphygmocor is one of the device which is not only measuring the pulse wave velocity (PWV) but also pulse wave analysis (PWA) (Laurent *et al.*, 2006).

1.2.4 Pulse Wave Analysis (PWA)

The amount of augmentation pressure is quantified in terms of the relative change over the whole pulse. For PWA, the tonometer will be placed and compressed gently on the radial artery until a consistent pressure waveform is displayed

between the upper and lower display limits and the data will be captured. From peripheral measurements, the PWA software derives the central aortic blood pressure waveform and a range of central arterial indices of ventricular – vascular interaction will be displayed. Once the early systolic shoulder (peak, P1) or the late systolic shoulder (P2) are identified, the difference between P1 and P2 will be expressed as a percentage of the pulse pressures which is calculated as augmentation index (AIx) (Mackenzie *et al.*, 2002; Sandy *et al.*, 2006).

The AIx was analysed in terms of the relationship to pulse wave reflection and global arterial stiffness. Comparison between AIx and PWV has shown a significant association, with a significant but relatively weak positive correlation found between AIx and aortic PWV ($r=0.29$, $p<0.005$) (Brown, 1999).

1.2.5 Pulse Wave Velocity (PWV)

PWV is the speed at which the forward pressure is transmitted from the aorta through the vascular tree. It is calculated by measuring the time taken for the arterial waveform to pass between two points with a measured distance apart and involves taking readings from two sites. PWV is measured when the tonometer placed and compressed gently on the carotid and femoral artery with ECG electrodes attached to the subject's chest area. The analysis will be done by the software and reading will be shown on the screen (Mackenzie *et al.*, 2002; Sandy *et al.*, 2006).

PWV is associated with wave reflection phenomenon of the central aortic waveform obtained by means of a transfer function from peripheral recordings of the arterial pulse. Reproducibility assessed through the Bland-Altman method with calculation of the repeatability coefficient was, following intraobserver comparison, for brachial PWV: 1.64m/sec (for a mean value of 8.65±1.58 m/sec); and for aortic PWV:2.34m/sec (for mean value of 8.15±3.01 m/sec). Corresponding data for between-observer values were 2.18m/sec and 2.50 m/sec, respectively (Wilkinson *et al.*, 1998).

1.2.6 Effect of arterial stiffness on glaucoma

Low arterial elasticity is associated with increased risk of hypertension (Liao *et al.*, 1999) and untreated hypertension may accelerate the rate of large arterial stiffness and thus perpetuate vicious cycle of accelerated hypertension and further stiffen the arteries (Franklin *et al.*, 1997).

Studies have shown strong association of arterial stiffness and atherosclerosis (Hirai *et al.*, 1989; van Popele *et al.*, 2001). Atherosclerosis is a chronic, progressive systemic disease which normally develops slowly with formation of fatty streak and atherosclerotic plaque. The lesion can cause blood flow limitation with either lumen narrowing or occlusion of the vessel due to rupture of the plaque with thrombus formation (Davies, 1995).

Arterial stiffness was also found to be associated with higher cardiovascular mortality such as heart failure and stroke (Blacher *et al.*, 1999; Sutton-Tyrrell *et al.*, 2005) and chronic kidney disease (Baumann *et al.*, 2014). Although the relationship between arterial stiffness and OAG has been reported, the answer is still inconclusive.

There are few studies regarding association of glaucoma with arterial stiffness. Siasos et al (2011) found out POAG patients had increased arterial stiffness, impaired endothelial dysfunction and increased inflammatory status (Siasos *et al.*, 2011). It is interesting to discover that retinal arteriolar and venular diameters are found narrowed during normal aging due to age associated vascular rigidity and atherosclerosis (Leung *et al.*, 2003). On the other hand, Chiba et al (2008) reported that systemic arterial stiffness seems not to be strongly associated with glaucoma (Chiba *et al.*, 2008). Moreover, another study showed there was only minor difference of waveform parameters between glaucoma and normal participants which did not show any relationship between arterial stiffness and glaucoma in study by Graham (Graham *et al.*, 2013).

Despite well controlled IOP, glaucoma still progress in significant number of patients. Vascular factor has been suggested decades ago but yet little is known. Adequate ocular blood flow is as important as reduction of IOP in preventing further glaucomatous damage.

The purpose of the study is to focus on vascular changes especially arterial stiffness as risk factors for disease progression and try to advocate an additional route in the pathogenesis of glaucomatous optic neuropathy. A combination of high IOP and inadequate ocular perfusion may theoretically accelerate the glaucomatous optic neuropathy lead to rapid progression and more severe disease. To the best of our knowledge, study of arterial stiffness on severity and progression of POAG is very limited. Early detection of systemic arterial stiffness might reduce the severity and progression of glaucoma by targeting and emphasizing modifiable habits earlier.

2.1 General Objective

To evaluate the effects of arterial stiffness on severity and progression of primary open angle glaucoma (POAG).

2.2 Specific Objectives

1. To compare the mean of arterial stiffness between POAG patients and controls.
2. To compare the mean of arterial stiffness on severity of POAG.
3. To compare the mean of arterial stiffness on progression of POAG.