Triple Vessel Coronary Artery Disease and Retinal Nerve Fibre Layer Thickness

Dear Editor,

Atherosclerosis is a pathological process that leads to blockage of the coronary artery and causes systemic vascular insufficiency. Coronary artery disease (CAD) is identified as a potential cause of insufficiency in optic nerve head (ONH) perfusion. Ischaemia due to vascular insufficiency in the ONH has been postulated as a potential cause of retinal nerve fibre layer (RNFL) damage.[1] Structural damage to the RNFL may lead to the thinning of this important layer and cause functional impairment of the visual field. Early detection of RNFL damage is important in prevention of blindness due to many ocular diseases especially glaucoma. This study aimed to compare the RNFL thickness in patients with triple vessel coronary artery disease (3VCAD) with normal subjects.

Materials and Methods

A cross-sectional study was conducted from April 2012 to September 2013 involving patients with 3VCAD attending a cardiothoracic clinic in Penang General Hospital (PGH) and Hospital Universiti Sains Malaysia (HUSM). 3VCAD is defined as more than 50% of stenosis involving 3 major epicardial vessels based on coronary angiogram. Control subjects were recruited from the employee group at HUSM and the Department of Ophthalmology. Exclusion criteria included subjects with glaucoma (those who have glaucomatous visual field changes and optic neuropathy) or glaucoma-suspect (defined as suspicious optic disc but do not fulfill criteria of glaucoma);[2] subjects with ocular hypertension (those with intraocular pressure of more than 21 mmHg);[3] subjects with evidence of any form of optic neuropathy or retinal dystrophy, history of pan-retinal photocoagulation laser therapy, or high axial myopia with axial length of more than 25 mm; and subjects diagnosed to have autoimmune or thyroid disease, presence of media opacity that compromises signal strength of less than 6/10 during optical coherent tomography (OCT) scanning or inability to obtain 2 reliable visual fields (fixation losses >20%, false-positive responses >33%, false-negative responses >33%) or inability to obtain 3 adequate OCT images.

Associated systemic diseases and risk factors like hypertension (systolic blood pressure >120 mmHg, diastolic blood pressure >80 mmHg),[4] diabetes mellitus (fasting blood sugar = 7 mmol/l),[5] dyslipidaemia (total cholesterol >5.2 mmol/l),[6] and smoking history were documented. The complete ophthalmic evaluations included Humphrey visual field analysis and RNFL thickness and ONH parameters assessment using OCT (Cirrus, Dublin, USA). Only the image with the best signal strength of more than 6/10 was selected. The right eye was chosen for data analysis if both eyes were eligible. Figure 1 shows examples of OCT images of 3VCAD from 3 patients.

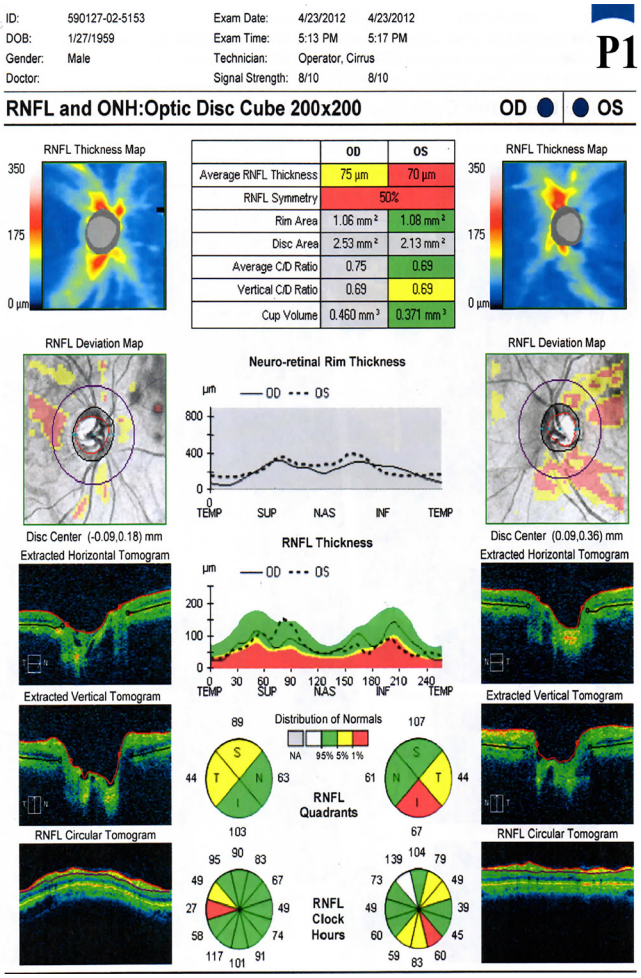


Fig. 1. OCT images showing RNFL thickness and ONH parameters of patients with 3VCAD: P1, P2 and P3. OCT: Optical coherent tomography; ONH: Optic nerve head; RNFL: Retinal nerve fibre layer; 3VCAD: Triple vessel coronary artery disease.

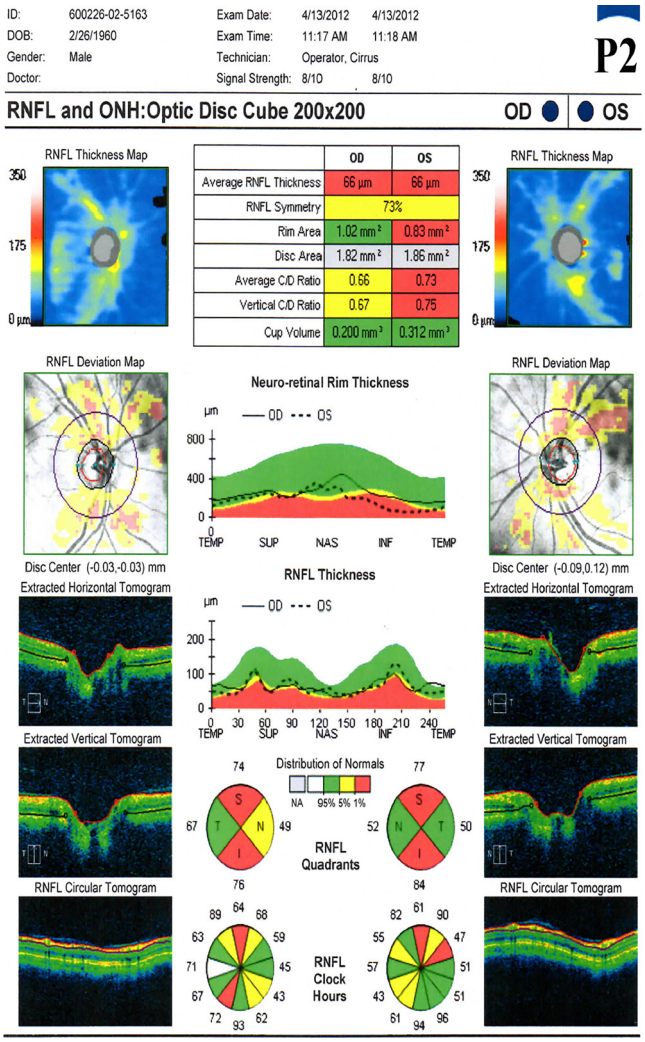
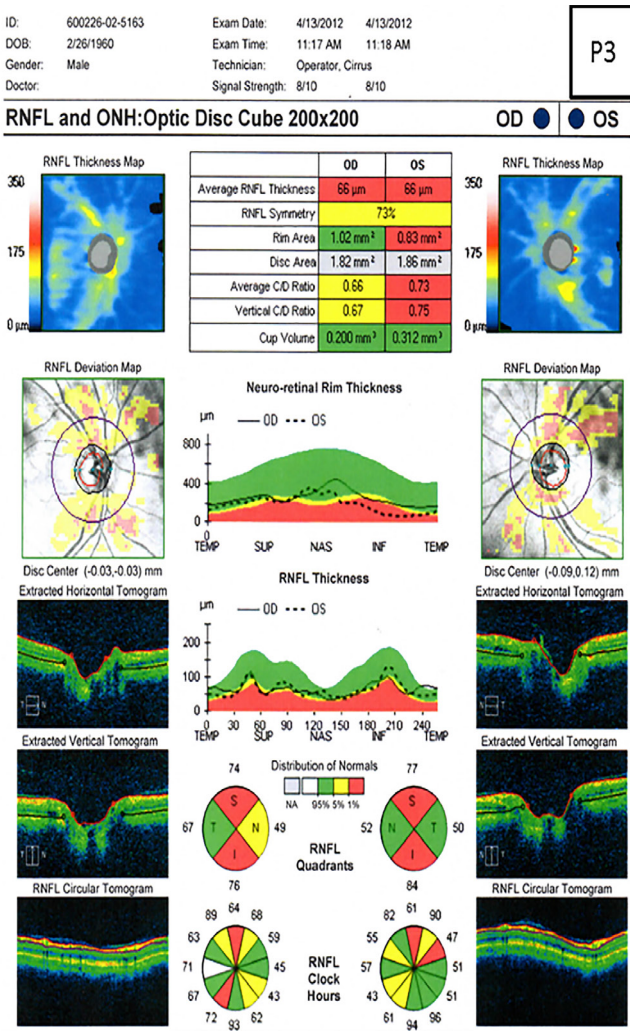


Fig. 1 (Cont'd). OCT images showing RNFL thickness and ONH parameters of patients with 3VCAD: P1, P2 and P3. OCT: Optical coherent tomography; ONH: Optic nerve head; RNFL: Retinal nerve fibre layer; 3VCAD: Triple vessel coronary artery disease.



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Statistical analysis was conducted using Predictive Analytic Software (PASW) 20. Demographic data was analysed with descriptive statistics and reported as mean, standard deviation, and percentage. Baseline univariate comparisons between the study group and the controls were performed using an independent t-test and Pearson chi-squared test. The difference in ocular and ONH RNFL parameters between 3VCAD patients and controls were analysed using an independent t-test. Confounding factors were adjusted using the analysis of covariance (ANCOVA) method.

Results

A total of 59 3VCAD patients and 60 controls were recruited. Most 3VCAD patients were male (81.4%) and were significantly older (mean age = 59.1) (Table 1). Most of these patients were active or ex-smokers (62.7%) with systemic diseases, hypertension (88.1%), dyslipidaemia (89.8%), and diabetes (44.1%) (Table 1). They had significantly higher mean baseline intraocular pressure (IOP) (16.1 mmHg vs 14.68 mmHg, $P = 0.011$), higher mean vertical cup-to-disc ratio (VCDR) ($P < 0.001$), and thinner mean ONH RNFL thickness ($P < 0.001$) (Table 1). Age, sex, race, and axial lengths were identified as confounding factors for the ONH RNFL thickness in general populations. Other confounding factors such as systemic hypertension, diabetes mellitus, hyperlipidaemia and smoking habit were also included. There was a significant difference in the mean RNFL between the 3VCAD and control groups without controlling these variables. The mean

Table 1. Comparison of Demographic Data, RNFL Thickness and ONH Parameters between 3VCAD and Control Groups

	3VCAD n = 59	Control n = 60	*P* Value
Age (years)			
Range	33 – 79	19 – 75	
Mean (SD)	59.1 (9.0)	54.1 (10.9)	0.007*
Sex (n, %)			
Male	48 (81.4)	20 (33.3)	<0.001
Female	11 (18.6)	40 (66.7)	<0.001
Race (n, %)			
Malay	38 (64.4)	52 (86.7)	0.003
Chinese	13 (22.0)	8 (13.3)	0.003
Indian	8 (13.6)	0	0.003
Systemic diseases (n, %)			
Hypertension	52 (88.1)	15 (25.0)	<0.001
Diabetes mellitus	26 (44.1)	10 (16.7)	0.001
Hyperlipidaemia	53 (89.8)	17 (28.3)	<0.001
Smoking			
Smoker	37 (62.7)	6 (10.0)	<0.001
Non-smoker	22 (37.3)	54 (90.0)	
Baseline IOP (mmHg)			
Mean ± SD	16.1 ± 3.03	14.7 ± 2.93	0.011*
Axial length (mm)			
Mean± SD	23.38 ± 0.83	23.08 ± 0.85	0.070*
RNFL thickness (μm)			
Range	66 – 129	68 – 126	
Mean ± SD	91.29 ± 12.43	100.20 ± 11.47	<0.001*
ONH disc area (mm^2)			
Range	1.23 – 3.05	1.34 – 3.23	
Mean ± SD	2.09 ± 0.42	2.16 ± 0.37	0.326*
ONH rim area (mm^2)			
Range	0.68 – 2.24	0.94 – 2.00	
Mean ± SD	1.29 ± 0.29	1.38 ± 0.23	0.052*
vCDR			
Range	0.2 – 0.5	0.2 – 0.6	
Mean ± SD	0.39 ± 0.11	0.33 ± 0.06	<0.001*

IOP: Intraocular pressure; ONH: Optic nerve head; RNFL: Retinal nerve fibre layer; vCDR: Vertical cup-to-disc ratio; 3VCAD: Triple vessel coronary artery disease
*Independent t-test.
P <0.05, Pearson chi-squared test.

RNFL was significantly thinner in 3VCAD patients even after considering the confounding factors using ANCOVA analysis (*P* = 0.038) (Table 2).

Table 2. Comparison of Mean RNFL Thickness between 3VCAD and Control with Adjustment of Age, Sex, Race, Axial Length, Baseline IOP, Hypertension, Hyperlipidaemia, Diabetes Mellitus and Smoking

	Mean RNFL Thickness (μm)	Mean Difference (95% CI [LCI, UCI])	F-Stat	*P* Value
3VCAD (n = 59)	92.52 (89.10, 95.97)	-7.68 (-14.94, -0.42)	4.39	0.038
Control (n = 60)	98.99 (95.57, 102.41)			

CI: Confidence interval; IOP: Intraocular pressure; LCI: Lower confidence interval; UCI: Upper confidence interval; RNFL: Retinal nerve fibre layer; 3VCAD: Triple vessel coronary artery disease
P <0.05, analysis of covariance (ANCOVA) applied.

Discussion

In our study, mean RNFL was significantly thinner in 3VCAD patients. There was no reported impact of 3VCAD on ONH circulation except for the impact of coronary artery bypass graft (CABG) surgery on ONH RNFL thickness.[7] Buyukates et al found that the temporary interruption of systemic circulation during CABG causes a temporary reduction in RNFL thickness.[7] However, there is no evidence of insult to ONH caused by 3VCAD prior to the surgery. Thus, there is a possibility that it is an additional insult to preexisting neuronal damage due to the disease. Although the exact mechanism is not known, it has been postulated to be related to extensive systemic atherosclerosis in 3VCAD patients that affects not only the coronary arteries but also other circulatory systems including ONH circulation.[8]

ONH is well vascularised by dual blood supply, short posterior ciliary artery (SPCA) and the central retinal artery (CRA). Most of its supply is through end arterioles and its circulation is maintained by autoregulation, which is similar to other vital organs such as the brain and kidney.[9] Autoregulation is susceptible to impairment of ocular blood flow. Ischaemic insults and reperfusion injury of the ONH may occur in patients with 3VCAD patients during their episodes of angina. This may lead to acceleration of retinal ganglion cell apoptosis and structural changes of the ONH.[10] In addition, atherosclerosis, vasospasm and endothelial dysfunction may also impair the ONH perfusion.[11]

Selection of control subjects among employees of the hospital and institution was far from ideal and subject to biases.[12] Patients attending eye clinic for other ocular problems (such as pterygium or dry eye) can also have been recruited as control subjects. However, the problem in obtaining the proper history of systemic comorbidities and potential CADs in these patients may arise. Since most of our hospital staff and employees of our institution have been on regular medical check-up, it was more appropriate to recruit them as our control subjects. This may help in reducing the antecedent-consequent bias in a cross-sectional study.[12]

In this study, matching of confounders between 3VCAD patients and control subjects was not done. Matching may help eliminate (to a certain extent) any confounders; however, the main potential benefit of matching is a gain in efficiency.[13,14] Matching is more appropriate in case-control studies. Overmatching may also occur in matched studies.[13] In order to avoid spurious result that will not yield any information, the number of matching variables need to be minimal as possible.[13] Due to these reasons, we decided not to match the confounders between the 2 groups. We used multivariate analysis ANCOVA instead to eliminate the effect of potential confounders in this study.[14]

Although advancing age affects RNFL thickness and atherosclerosis severity,[15,16] the difference in mean ONH RNFL thickness between the 3VCAD and control groups is still significant after adjustment for age. Generally, RNFL thickness is affected by race, sex and axial length.[15,17] Systemic hypertension, diabetes mellitus and hyperlipidaemia increase the risk of CAD.[18,19,20] These systemic comorbidities may also affect RNFL thickness but the evidence is still inconclusive. Even after controlling all these confounders, there was significant thinner RNFL thickness in 3CVAD patients compared to control subjects.

Conclusion

3VCAD is associated with thinner RNFL. Thinner RNFL may be associated with the development of ocular diseases such as glaucoma or lead to accelerated damage of ONH in 3VCAD with pre-existing ocular disease. Ophthalmic screening is recommended for 3VCAD patients, especially in those with associated ocular disease, to prevent further insult to the ONH resulting in blindness.

Acknowledgement

The authors would like to thank the patients who participated in this study. This study was not financially supported by any grant.

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