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A spectrum of retinal vasculature measures and coronary artery disease

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ABSTRACT

Background and aims: We aimed to comprehensively describe a spectrum of retinal vessel measures including fractal dimension (D_f) and their associations with indices of coronary artery disease (CAD) extent and severity, as well as hypertension and diabetes.

Methods: The Australian Heart Eye Study (AHES) is an observational study that surveyed 1680 participants presenting to a tertiary referral hospital for the evaluation of potential CAD by coronary angiography. A range of newer retinal vessel geometric measures (D_f, curvature tortuosity, and branching angle) were quantified from retinal photographs using semi-automated software, the Singapore 'I' Vessel Assessment (SIVA) tool. A combined retinal score was constructed, aiming to assess the joint effect of multiple retinal vessel parameters on CAD, comprising of those variables that were most strongly significant in multivariate analysis - D_f, arteriolar curvature tortuosity, and retinal arteriolar calibre. CAD was objectively quantified using a range of measures obtained from coronary angiography.

Results: A total of 1187 participants had complete data on retinal vessel measurements and coronary vessel evaluation. Retinal vascular D_f and curvature tortuosity decreased with increasing age; women had significantly lower D_f than men ($p<0.003$). Straighter retinal vessels were associated with CAD extent and Gensini scores in multivariable analysis ($p<0.02$). Accounting for media opacity by sub-group analysis in pseudophakic patients, the combined retinal score was associated with stenosis greater than 50% in any coronary artery segment (vessel score) and obstructive coronary stenosis in all three main coronary arteries (segment score) ($p = 0.01$). Lower D_f and narrower arteriolar branching angle were associated with CAD vessel score ($p<0.03$). In sex-stratified multivariate analyses, straighter arterioles were associated with greater odds of CAD in men, and narrower venular branching angle was associated with CAD in women.

Conclusions: A range of retinal vessel measures were associated with CAD extent and severity. A sparser retinal microvascular network (smaller D_f) was associated with older age and female gender. After accounting for the impact of media opacity, retinal vessel measures were associated with more diffuse and severe CAD.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in Australia [1], despite numerous advances in cardiac intervention and management. Further advances may rely on better understanding of the underlying pathogenesis of CVD and the identification of novel risk factors. Most research on CVD has been focused on larger vessels - that is, the coronary arteries, which contribute towards the development of coronary artery disease (CAD). However, it has been increasingly recognised that coronary microvascular changes may also play a significant role in CAD pathogenesis [2,3].

The blood vessels of the retinal vasculature measure between 100 and 300 μm, which is typical of other microvascular systems

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[2]. The retinal vascular architecture requires optimal flow and function [4], thus deviations from this optimal state occur in disease processes. It has been proposed that these deviations may also be reflective of more generalised microvascular disease [5]. Based on this principle, the concept of fractal analysis was developed to provide a global assessment of the architecture of the retinal vascular network [6,7], in particular the bifurcations and density of small vessels. This concept has been applied in diverse biological structures [8], such as the branching patterns of retinal [9], coronary [10], and pulmonary arterioles [11], as well as biological rhythms such as cardiac arrhythmias [12,13].

Thus, retinal vascular geometric measures such as retinal vascular fractal dimension (D_f) have been used to quantify the global structure of the retinal circulation. Studies show that retinal vascular D_f is associated with coronary heart disease mortality [14], hypertension [15,16], diabetic retinopathy [17–19], chronic kidney disease [20], stroke [21–23], non-arteritic anterior ischemic optic neuropathy [24], and even rare diseases such as cerebral autosomal dominant arteriopathy with subcortical infarcts (CADASIL) [25].

There is some evidence that these retinal vascular geometric measures are associated with CVD risk factors, and may be predictive of clinical vascular events [26]. Cheung et al. found that smaller D_f, representing a “sparser” retinal vascular network, was associated independently with older age, elevated blood pressure, myopic refraction, and presence of cataract [5]. Smaller D_f has also been shown to be associated with stroke and cerebral microvascular disease [23,27]. Witt et al. also reported that people with incident ischaemic heart disease had impaired arteriolar tortuosity (both simple and curvature), independent of known cardiovascular risk factors, although this association was relatively weak [28].

Although retinal vascular measures such as D_f and their relationship with CVD risk factors have been studied in the general population, neither the relationship of these measures with angiographically defined CAD, nor their distribution in a cohort with high CVD risk has been studied. It is not known whether retinal vascular measures are different or similar in such patients. Furthermore, the concept of a combined retinal score has been proposed, which attempts to measure the relationships between the retinal vasculature and CAD using the joint effect of multiple vessel parameters [5,29,30]. It is as yet unclear whether a combined retinal score that incorporates several significant retinal vessel geometric measures may be associated with severity and extent of CAD.

The aims of this paper were to describe retinal vasculature measures including retinal vascular D_f, branching angle, and tortuosity in a cohort with high CVD risk and to determine whether these retinal measures are associated with quantitative measures of CAD.

2. Materials and methods

2.1. Study population and data collection

The Australian Heart Eye Study (AHES) is a clinical cross-sectional study, sample size $n = 1680$. The methodology for this study has been previously described [31–36].In brief, between June 2009 and January 2012, participants were drawn from one of the largest tertiary referral hospitals servicing the greater western Sydney area (Westmead Hospital, Sydney, Australia) These participants presented to the hospital to be assessed for potential CAD by coronary angiography.

All eligible patients presenting for assessment of suspected CAD were included in this study. All patients provided written informed consent to participate in the study. Patients with a history of coronary artery bypass graft or coronary artery stenting were excluded. These patients were excluded because the Gensini and extent scoring systems have not been validated in this group. Participants were also excluded if they had incomplete information on CAD variables.

Ethics approval for the AHES was obtained from the Western Sydney Local Health Network Human Research Ethics Committee (Westmead).

2.2. Assessment of retinal vessel geometric measures

This paper uses the term *retinal vessel geometric measures* to refer to such parameters as D_f, curvature tortuosity, and branching angle, which can be quantified by considering the geometric configuration of the retinal vascular tree.

All participants had digital retinal photographs taken after pharmacological mydriasis. Seven standard Early Treatment Diabetic Retinopathy Study (ETDRS) 45° fields were taken using a digital retinal camera (Canon CR-DGI, Tokyo, Japan). For the purposes of the SIVA software, the disc-centred image was used.

Retinal vascular calibre measurements for the right eye of each participant were used. Left eye measurements were used if right eye photographs were not gradable. Two graders, masked to participant identity and characteristics, were used to grade fundus photographs for retinal vessel geometric measures [15,37].

A semi-automated computer-assisted program (Singapore I Vessel Assessment, version 1.0; National University of Singapore, Singapore) was used to quantitatively assess a range of retinal vascular geometric measures from digital fundus photographs. Fig. 1 shows the SIVA user interface for quantification of retinal vessel geometric parameters from a fundus photograph of patients from the AHES who had low, medium, and high D_f, respectively.

In brief, the software automatically detected and traced the optic disc and set the grading grid on the fundus photograph. It then automatically traced peripheral vessels, with manual vessel tracking required to ensure complete each tracing, and to check the accurate classification of vessels as either arterioles or venules. Vessel calibre was also manually checked along the length of each vessel. The measured area was defined within the region between 0.5 and 2.0 disc diameters away from the disc margin (zone C) [5].

Retinal vascular D_f was calculated from line tracings of the retinal vessels using the box-counting method, which divided each photograph into a series of squares of various side lengths [5]. D_f was defined as the gradient of logarithms of the number of boxes and the size of those boxes [16,38]. The more complex the branching pattern, the greater the D_f.

Curvature tortuosity was derived from the integral of the curvature square along the path of the vessel, normalised by the total path length [39]. This takes into account bowing and points of inflection [40], in contrast with simple tortuosity, which fails to distinguish between increased length due to bowing and that due to multiple points of inflection [28]. The straighter the vessel, the lower the tortuosity value [40]. Retinal arteriolar tortuosity and retinal venular tortuosity are a measure of the average tortuosity of the arterioles and venules in the eye, respectively (Fig. 2).

Retinal vascular branching angle was defined as the first angle subtended between two daughter vessels at each vascular bifurcation [27,40]. Retinal arteriolar branching angle and retinal venular branching angle quantify the average branching angle of arterioles and venules of the eye, respectively [5] (Fig. 3).

We quantified retinal vessel calibre using a computer-assisted program with high reproducibility, as has been previously described. [41,42], We measured the diameters of all arterioles and venules coursing through an area of 0.5–1 disc diameter surrounding the optic disc based on a standard protocol [43]. The Knudtson-Hubbard formula was used to calculate average retinal