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Associations between retinal microvascular structure and the severity and extent of coronary artery disease

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ABSTRACT

Objective: Microvascular mechanisms are increasingly recognized as being involved in a significant proportion of coronary artery disease (CAD) cases, but their exact contribution or role is unclear. We aimed to define the association between retinal microvascular signs and both CAD extent and severity.
Methods: 1120 participants of the Australian Heart Eye Study were included. Retinal vessel caliber was measured from digital retinal images. Extent and severity of CAD was assessed using several approaches. First, a simple scoring classifying participants as having one-vessel, two-vessel, and three-vessel disease was used. Gensini and Extent scores were calculated using angiography findings.
Results: After multivariable adjustment, significantly narrower retinal arteriolar caliber in women (comparing lowest versus highest quartile or reference) and wider venular caliber in men (comparing highest versus lowest quartile or reference) were associated with 2-fold and 54% higher odds of having at least one stenosis ≥50% in the epicardial coronary arteries, respectively. Women in the third versus first tertile of retinal venular caliber had 92% and ~2-fold higher likelihood of having higher Gensini and Extent scores, respectively. Women in the lowest versus highest tertile of retinal arteriolar caliber had greater odds of having higher Extent scores, OR 2.99 (95% CI 1.45–6.16). In men, non-significant associations were observed between retinal vascular caliber and Gensini and Extent scores.
Conclusions: An unhealthy retinal microvascular profile, namely, narrower retinal arterioles and wider venules was associated with more diffuse and severe CAD among women.

1. Introduction

Coronary heart disease (CHD) remains the leading cause of death worldwide and leads to substantial economic burden [1]. Traditional risk factors such as smoking, hypertension hyperlipidemia and diabetes are thought to explain most CHD [2,3], although, 15–20% of those with CHD have no identified traditional risk factors and miss the opportunity for primary prevention [3–5].

The retinal vessels can be observed directly and non-invasively, and are therefore, clinically useful for assessing the systemic microvasculature [6,7]. Recent studies have shown that changes in retinal microvascular diameter (narrower retinal arteriolar caliber and wider venular caliber) are associated with CHD risk factors, including obesity, components of the metabolic syndrome, systemic inflammation and endothelial dysfunction, and hypertension [8–15]. Retinal arteriolar narrowing is strongly correlated with high blood pressure [16] and retinal venular widening is a marker for endothelial dysfunction, hyperglycemia and inflammation [17–20]. Moreover, changes in retinal vessel caliber appear to predict future vascular events [6,21,22]. However, to our best knowledge, the relationship between changes in the retinal microvascular structure and severity and extent of coronary artery disease (CAD) estimated by quantitative coronary angiography, has yet to be thoroughly investigated.

The present study was undertaken to assess whether retinal microvascular signs are independently associated with indices of CAD severity and extent, among patients presenting with suspected CAD. The data from this study will add to new knowledge by determining the potential value of retinal microvascular changes as

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prognostic markers of CHD risk, and whether there is a role for non-invasive retinal imaging of CHD suspects that could add to or precede coronary angiography.

2. Methods

2.1. Participants

Between June 2009 and January 2012 we approached 2627 symptomatic patients presenting to Westmead Hospital for assessment of suspected CAD. Biochemical, angiographic, clinical data, peripheral arteriolar wave form analysis, pulse wave velocity, ankle brachial pressure index, peripheral and invasive blood pressure measurements, echocardiography, electrocardiography, visual acuity and retinal photography data were collected on 1680 participants. Of the 1680 examined in this study a total of 560 participants were excluded. Patients with a previous history of coronary artery bypass grafting (CABG; $n = 191$) or previous coronary artery stent ($n = 207$) were not included. We excluded CABG and previous stented patients as the scoring system used has not been validated in this group. Stented segments may look normal on angiography and as such, any disease is under-estimated. The Gensini and Extent score is not a valid method of examining CABG patients. If there was incomplete information of retinal vessel measures or absent Gensini or Extent scores, these participants were excluded. Participants compared to non-participants were more likely to be Caucasian, and a smoker, but less likely to have hypertension and had lower systolic BP and MABP levels (Online Supplementary Table 1). Ethics approval was obtained from the Western Sydney Local Health Network Human Research Ethics Committee.

2.2. Medical history

A 252-item questionnaire was used to obtain medical history, cardiovascular and familial risk factors. This included history of angina, myocardial infarction or angiography and intervention (coronary artery stent or coronary artery bypass graft, CABG), previous stroke, transient ischemic attack (TIA), hypertension, hypercholesterolemia, diabetes mellitus, and current management of these chronic conditions, current medications, smoking status and alcohol consumption. Previous history of CHD (AMI, CABG) and/or coronary artery stent was determined by self-report and/or review of previous admissions.

2.3. Coronary angiography

Indications for coronary angiography in our population were the investigation of suspected ischemic chest pain in people with and without a prior history of coronary artery disease, stenting or coronary artery bypass grafting, unstable angina, and/or acute myocardial infarction. All patients approached for the study were already internally and externally referred and consented for invasive coronary angiography. Relative contraindications for invasive coronary angiography include pre-existing renal impairment and contrast allergy. However these were not absolute and coronary angiography was performed if the risk benefit ratio was favorable.

Routine diagnostic coronary angiography was performed after fasting via a femoral or radial approach using a catheter of known dimension (5Fr to 7Fr). The technique employed was determined by vascular accessibility of the patient and operator preference. Selective coronary injections of Ultravist (Schering) were filmed in standard projections with a Siemens Bi-Plane radiographic unit (Siemens Healthcare, Germany). All angiograms were filmed at 15 frames/second. Cine runs were stored at the time of acquisition in DICOM format, 512 × 512 pixels at 8 bit resolution (256 grayscales).

All angiograms were analyzed offline by a trained cardiologist blinded to the results of the adjunctive investigations and retinal grading. Two orthogonal views were examined in end-diastole to maximize contrast enhancement and vessel diameter. The image with the most severe stenosis was used for each evaluated segment of the coronary arteries. The coronary artery segments were defined using the Syntax system which divides the arterial tree into 16 parts [23]. For each segment, the severity of obstruction was documented using several grades: normal, 1–25%, 25–50%, 50–74%, 75–99% and 100% (occluded). Each lesion that was visually scored as greater than 50% luminal obstruction in a vessel that was ≥1.5 mm diameter was further analyzed using quantitative coronary analysis (QCA) [24]. QCA was performed using validated computerized edge-detection software (QCAPLUS, Sanders data Systems, Palo Alto, California, USA). The catheter of known diameter was used for calibration. The proximal and distal ends of the stenotic segment in an end-diastole frame were determined by the examiner. The percent diameter of stenosis was computed by the software. Coronary angiograms were scored according to three methods:

1) Vessel and segment score: A vessel score was calculated based on the number of vessels with significant obstructive coronary disease. A definition of 50% stenosis characterized significant vessel disease [25]. This definition was used for the left main coronary artery, right coronary, left anterior descending and left circumflex arteries. Scores ranged from 0 to 4, depending on the vessels with greater than 50% stenosis [26]. Left main artery stenosis was scored as double vessel disease. The segment score was reported based on the number of obstructive lesions present in the 16 segments.
2) Gensini score: This has been described previously [27]. Briefly, the coronary arterial tree was divided into segments with multiplying factors according to the functional importance of any given segment (5 for the left main trunk to 0.5 for the most distal segments) and the % reduction in luminal diameter of each narrowing was assigned a score (0, 1, 2, 4, 8, 16 or 32 according to the degree of stenosis). The sum of the scores of all segments gives the Gensini score, placing emphasis on the severity of the disease [26].
3) Extent score: The Extent score defines the proportion of the coronary arterial tree involved by angiographically detectable coronary atheroma [28]. The proportion of each vessel involved by atheroma, identified by lumen irregularity, was multiplied by a factor (related to the length of that vessel) for each vessel. Scores were added to give a total score out of 100. This percentage represents the proportion of the coronary intimal surface area containing coronary atheroma [26].

To assess inter-observer and intra-observer variation in the coronary angiography analysis, 40 random cases were selected. Angiograms were blinded as to patient name, date of study, and diagnosis. Moreover, angiograms were interpreted in the present study six months to one year after they had been performed. We used concordance correlation coefficients (CCC) to evaluate reproducibility or inter-observer reliability of Gensini and Extent scores.

2.4. Retinal vascular caliber assessment

Participants had dilated, digital photographs taken of the optic disc and macula of both eyes using a Canon 60° fundus camera (Model CF-60DSi, Canon Inc., Tokyo, Japan) with an attached digital camera (Model 1DSmkIII, Canon Inc., Tokyo, Japan). Retinal vascular caliber measurements for the right eye of each participant were used. Left eye