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ORIGINAL ARTICLE

Retinal Vascular Geometry and the Prevalence of Atrial Fibrillation and Heart Failure in a Clinic-Based Sample

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Background We aimed to examine the cross-sectional association between a range of retinal vascular geometric variables and the prevalence of atrial fibrillation (AF) and heart failure.

Methods The Australian Heart Eye Study (AHES) surveyed 1,680 participants presenting to a tertiary referral hospital for the evaluation of potential coronary artery disease by coronary angiography. Retinal vascular geometric variables (tortuosity, branching, and fractal dimension) were measured from retinal photographs using a computer-assisted program (Singapore I Vessel Assessment). Atrial fibrillation was determined based on a combination of: self-reported history of AF; self-reported use of rate-control and anti-arrhythmic medications; and/or screening electrocardiogram. Self-reported echocardiography-confirmed heart failure was also documented.

Results A total of 1,169 participants had complete information on retinal vascular geometric variables and AF and of these 104 (8.9%) had AF. Participants in the second tertile of fractal dimension (D_f) compared to those in the highest tertile (reference group), had 92% increased likelihood of having AF after multivariable adjustment. A threshold effect for D_f was identified, and participants below versus those above a D_f threshold value of 1.472, had greater odds of having AF: multivariable-adjusted OR 1.85 (95% CI 1.03–3.31). Measures of retinal tortuosity and branching were not associated with AF. Retinal vascular geometric variables were also not associated with prevalence of heart failure.

Conclusions A sparser retinal microvascular network (lower D_f) was independently associated with greater likelihood of AF. Further studies are needed to investigate whether temporal changes to the retinal vascular geometry are predictive of AF in the longer term.

Keywords Atrial fibrillation • Retinal vascular geometry • Fractal dimension • Heart failure

Introduction

Heart failure and atrial fibrillation (AF) are two conditions that are likely to dominate the next 50 years of cardiovascular care. Both are becoming increasingly prevalent and are associated with high morbidity, mortality, and health care cost [1]. These are closely inter-related with similar risk factors (e.g. smoking, obesity, diabetes, and hypertension) and shared pathophysiology [1,2].

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The microvasculature of the retina is a vascular bed that can be easily viewed and non-invasively imaged [3], and its association with risk of AF and heart failure has been previously studied. For instance, we showed that retinal vascular calibre and diabetic retinopathy were not associated with the prevalence of AF in a clinic-based cohort [4]. This confirmed findings from the Chronic Renal Insufficiency Cohort study, where no significant associations were observed between retinopathy grade and prevalent AF [5]. In regards to heart failure, we found a wider retinal arteriolar diameter to be significantly and independently associated with prevalent heart failure [6]. This association was significantly stronger among participants with diabetes compared to without diabetes [6].

Currently, the relationship between the retinal microvascular architecture or retinal branching network and likelihood of AF and heart failure remains largely unexplored. The retinal vascular architecture requires optimal flow and function, 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 [7]. Information regarding the branching pattern or density of the retinal microvascular network can be best characterised by fractal analysis [8,9]. Retinal fractal dimension (D_f) is a single 'global' measure of the branching pattern of retinal vessels as a whole, and was also earlier found to be associated with higher blood pressure (BP) [9], and coronary heart disease mortality [10].

In our cohort of patients presenting with suspected coronary artery disease (CAD) to a tertiary referral hospital, we aimed to investigate the independent, cross-sectional relationship between a range of newer retinal vessel geometric measures (retinal vascular D_f, branching angle and tortuosity) with the prevalence of AF and heart failure. Potential links between retinal vascular geometry and AF and heart failure would have important clinical implications, as individuals with early changes in the retinal microvascular architecture could be screened or monitored for development of these heart conditions.

Methods

Study Participants

Between June 2009 and January 2012, 2,627 symptomatic patients presenting to Westmead Hospital for assessment of suspected CAD were approached for this cross-sectional study. Subsequently, 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 1,680 participants [11]. Ethics approval was obtained from the Western Sydney Local Health Network Human Research Ethics Committee.

Assessment of Retinal Vessel Geometric Measures

This report 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 (7) standard Early Treatment Diabetic Retinopathy Study (ETDRS) 45° fields were taken using a digital retinal camera (Canon CR-DGi, Tokyo, Japan).

Two graders, masked to participant identity and characteristics, were used to grade fundus photographs for retinal vessel geometric measures [12,13]. 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. In brief, the software automatically detected and traced the optic disc, set the grading grid on the fundus photograph and automatically traced the peripheral vessels. Manual vessel tracking was performed to ensure complete tracings, and to confirm 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 [7].

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 [7]. D_f was defined as the gradient of logarithms of the number of boxes and the size of those boxes [9,14]. 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 [15]. This takes into account bowing and points of inflection [16], in contrast with simple tortuosity, which fails to distinguish between increased length due to bowing and that due to multiple points of inflection [17]. The straighter the vessel, the lower the tortuosity value [16]. Retinal arteriolar tortuosity and retinal venular tortuosity are a measure of the average tortuosity of the arterioles and venules in the eye, respectively. Retinal vascular branching angle was defined as the first angle subtended between two daughter vessels at each vascular bifurcation [16,18]. Retinal arteriolar branching angle and retinal venular branching angle quantify the average branching angle of arterioles and venules of the eye, respectively [7].

Assessment of AF

Atrial fibrillation status was determined by a combination of methods including: (1) current history of AF as reported by the patient on the baseline medical history questionnaire; (2) current use of rate-control and anti-arrhythmic medications as reported by the patient in the current medications section of the questionnaire; and (3) AF as detected by on screening electrocardiogram when the patient was presented to the hospital [4]. However, in the current study we were unable to determine precisely for each patient the type of AF, whether it was paroxysmal, persistent or permanent AF.

Assessment of Heart Failure

A comprehensive questionnaire was used by study personnel to obtain a detailed medical history, including year of heart failure diagnosis, classification of heart failure (NYHA Class I–IV), and treatment for heart failure including fluid restriction (litres per day), biventricular pacemakers, and medications. Heart failure prevalence was defined as a positive response to both questions ''When was it diagnosed?'' and ''Was diagnosis confirmed with transthoracic echocardiography or transoesophageal echocardiography'' [6]. Other information collected included past cardiovascular events, cardiovascular risk factors, other medical conditions, drug and alcohol history, and history of past angiography and/or interventions (coronary artery stent or coronary artery bypass graft).

Assessment of Covariates

Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Diastolic and systolic blood pressures and heart rate were measured, with a single reading, from the right arm with an Intellisense^{TM} OMRON digital automatic blood pressure monitor in the supine position. (Model HEM-907; OMRON Healthcare, Singapore). Biochemical data, including fasting blood sugar, $HbA1_c$ level, and fasting cholesterol and triglyceride levels were collected from participants' medical records.

Statistical Analysis

SAS statistical software (SAS Institute, Cary, NC, USA) version 9.4 was used for analyses including t-tests, $\chi 2$-tests and logistic regression. We analysed the retinal vascular geometric variables as categorical (i.e. tertiles) variables. Logistic regression models were used to determine whether associations exist between retinal vessel geometric measures (D_f, curvature tortuosity, and branching angle) and prevalence of AF and heart failure, adjusting for (i) age and sex; and then further adjusting for (ii) ethnicity, diabetes, BMI, and systolic blood pressure. Estimates are presented as odds ratio (OR) and 95% confidence intervals (CI).

Results

Of the 1,680 participants examined, photographs from 1,623 subjects (96.6%) were analysed after excluding images of poor quality. We then further excluded those images: (a) without at least four large gradable arterioles or venules; (b) without arteriolar or venular bifurcations within the measured area or optical artefact at the measured zone; and (c) retinal images with different camera settings, leaving 1,187 (70.7%) participants. A further 18 participants were excluded as they did not have information on the presence or absence of AF, leaving 1,169 participants for cross-sectional analysis. Of the 1,169 participants, 104 (8.9%) participants had AF.

Table 1 **Demographic and clinical characteristics of participants, stratified by presence or absence of atrial fibrillation (AF).**

Characteristics	With AF (n = 104)	Without AF (n = 1065)	P-value
Age, *yrs*	67.6 (10.0)	60.3 (11.6)	<0.0001
Male	74 (71.2)	818 (76.8)	0.20
Ethnicity			
Caucasian	85 (81.7)	733 (68.8)	
East Asian	1 (1.0)	60 (5.6)	
Southeast Asian	1 (1.0)	91 (8.5)	0.005
Middle Eastern	7 (6.7)	103 (9.7)	
Others	10 (9.6)	78 (7.3)	
Alcohol consumption			
Never	26 (25.2)	297 (28.2)	
Occasionally	58 (56.3)	613 (58.2)	0.38
Frequently	19 (18.5)	143 (13.6)	
BMI, kg/m^2	30.9 (6.6)	29.4 (5.5)	0.03
Systolic BP (mmHg)	123.6 (18.5)	127.1 (19.7)	0.09
Total cholesterol	4.09 (1.2)	4.62 (1.1)	0.0003
HbA1c	7.50 (2.2)	7.10 (1.8)	0.30
History of diabetes	40 (38.5)	341 (32.1)	0.18
Self-reported sleep apnoea	13 (12.36)	108 (10.4)	0.48
Reported statin use	59 (56.7)	507 (47.6)	0.08
Reported anti-hypertensive use	83 (79.8)	642 (60.3)	<0.0001

Abbreviations: BMI, body mass index; BP, blood pressure.
Data are presented as mean (±SD) or n (%).

Participants with AF compared to those without were more likely to be older, Caucasian, have higher BMI, and use statins, and also have lower total cholesterol (Table 1). Further, 894 participants who were examined had complete information on heart failure and retinal vascular geometry and of these, 62 (6.9%) had heart failure. Participants with heart failure compared to those without were more likely to be older, use statins and anti-hypertensive medications, and have sleep apnoea and lower total cholesterol (Table 2).

Of all the retinal vascular geometric measures analysed, only D_f was independently associated with the prevalence of AF (Table 3). Specifically, those participants in the second tertile of D_f compared to those in the highest tertile (reference group), had 92% increased likelihood of having AF after accounting for potential confounders (Table 3). D_f tertile analysis indicated that there is likely to be a threshold between the second and third tertiles, hence, we tested this using a method previously described by Ulm [19]. Applying this method allowed us to identify a threshold value of 1.472 for D_f, and participants who were below this threshold value for D_f compared to those above this threshold had greater likelihood of having AF: multivariable-adjusted OR 1.85 (95% CI 1.03–3.31). Figure 1 contrasts two eyes, one with a sparse retinal vasculature (D_f <1.472) and the other with a more dense retinal vasculature pattern (D_f >1.472). Table 4 shows that there was no significant association between retinal vascular geometric variables and prevalence of heart failure.

Discussion

Our novel study aimed to establish whether quantitative assessment of geometric measures of the retinal vasculature could provide important additional prognostic information in patients with AF and heart failure. Retinal vascular geometry was not independently associated with the prevalence of heart failure in this cohort. However, participants who had reduced D_f were more likely to experience AF even after accounting for factors such as age, sex, weight, BP, and diabetes.

We speculate that the lack of an association between retinal vascular geometric variables and prevalent heart failure may be due to the small number of participants with heart failure which could have led to inadequate statistical power to detect any modest associations with some of the retinal vessel geometric measures. Nevertheless, we observed that those participants who had suboptimal retinal vascular branching complexity (sparse retinal vasculature) as indicated by reduced D_f, were significantly more likely to have AF. The underlying mechanism(s) for this observation are less clear. Both suboptimal retinal vascular architecture and AF share similar underlying risk factors including hypertension and diabetes mellitus [1,2,7,20]. Given these inter-related risk factors, it is plausible that a reduction in retinal vasculature branching pattern complexity is associated with prevalence of AF.

Table 2 Demographic and clinical characteristics of participants, stratified by presence or absence of heart failure.

Characteristics	With heart failure (n = 62)	Without heart failure (n = 832)	P-value
Age, *yrs*	65.2 (10.3)	60.5 (11.6)	0.002
Male	42 (67.7)	626 (75.2)	0.19
Ethnicity			
Caucasian	43 (69.4)	569 (68.4)	
East Asian	3 (4.8)	43 (5.2)	
Southeast Asian	3 (4.8)	77 (9.3)	0.37
Middle Eastern	10 (16.1)	80 (9.6)	
Others	3 (4.8)	63 (7.6)	
Alcohol consumption			
Never	27 (45.8)	241 (29.2)	0.02
Occasionally	24 (40.7)	469 (56.9)	
Frequently	8 (13.6)	115 (13.9)	
BMI, kg/m^2	30.5 (6.2)	29.4 (5.6)	0.13
Systolic BP (mmHg)	122.1 (18.8)	126.7 (19.3)	0.07
Total cholesterol	4.01 (1.1)	4.62 (1.1)	0.002
HbA1c	7.2 (2.3)	7.1 (1.8)	0.93
Self-reported sleep apnea	15 (25.0)	72 (8.8)	<0.0001
Reported statin use	42 (67.7)	374 (45.0)	0.001
Reported anti-hypertensive use	53 (85.5)	492 (59.1)	<0.0001
History of diabetes	27 (43.6)	273 (32.9)	0.09

Abbreviations: BMI, body mass index; BP, blood pressure.
Data are presented as mean (±SD) or n (%).

Table 3 Association between tertiles of retinal geometric measures (D_f, curvature tortuosity, branching angle) and prevalence of atrial fibrillation.

Retinal vascular geometric measures	No. of cases/no. at risk	Prevalence of atrial fibrillation	
		Model 1 OR (95% CI)[a]	Model 2 OR (95% CI)[b]
Fractal dimension			
1st tertile	43/389	1.40 (0.77-2.53)	1.56 (0.84-2.89)
2nd tertile	42/390	**1.85 (1.05-3.29)**	**1.92 (1.06-3.51)**
3rd tertile	19/390	1.0 (reference)	1.0 (reference)
Arteriolar tortuosity			
1st tertile	42/390	1.0 (reference)	1.0 (reference)
2nd tertile	30/388	0.73 (0.45-1.21)	0.68 (0.40-1.15)
3rd tertile	32/391	0.90 (0.55-1.48)	0.97 (0.57-1.63)
Venular tortuosity			
1st tertile	39/390	1.0 (reference)	1.0 (reference)
2nd tertile	33/389	0.95 (0.58-1.57)	0.93 (0.55-1.57)
3rd tertile	32/390	1.05 (0.63-1.75)	1.08 (0.63-1.85)
Arteriolar branching angle			
1st tertile	31/389	1.0 (reference)	1.0 (reference)
2nd tertile	41/390	1.46 (0.88-2.40)	1.38 (0.81-2.36)
3rd tertile	32/390	1.12 (0.66-1.89)	1.25 (0.72-2.17)
Venular branching angle			
1st tertile	40/389	1.0 (reference)	1.0 (reference)
2nd tertile	27/390	0.64 (0.38-1.07)	0.60 (0.34-1.06)
3rd tertile	37/390	0.84 (0.52-1.36)	0.94 (0.57-1.56)

Abbreviations: OR, odds ratio; CI, confidence intervals.
Bold values represent significant estimates ($p < 0.05$).
[a]Adjusted for age and sex.
[b]Further adjusted for ethnicity, systolic blood pressure, body mass index, and presence of type 2 diabetes.

Alternatively, emerging evidence suggests a significant role of inflammation and endothelial dysfunction in the pathogenesis of AF [21,22]. That evidence includes elevated serum levels of inflammatory biomarkers in AF subjects, and the expression of inflammatory markers in cardiac tissues of AF patients and animal models of AF [21]. Further, endothelial dysfunction, as demonstrated by impairment of flow-mediated dilatation and raised von Willebrand factor and E-

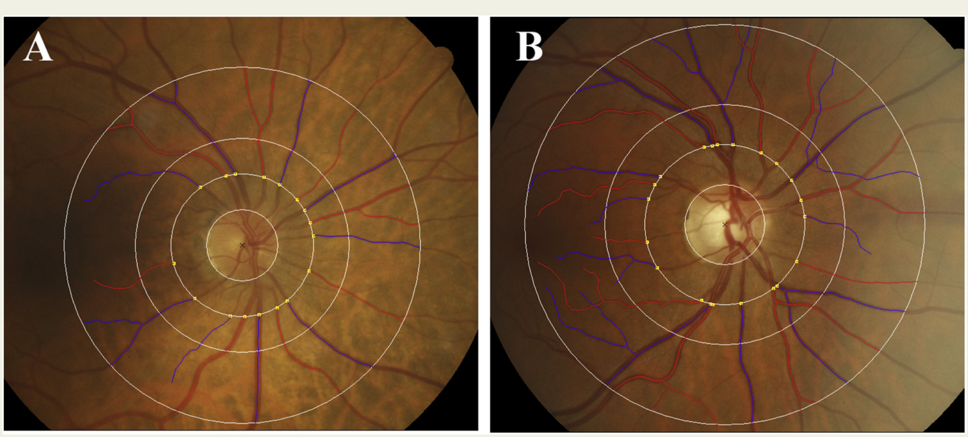

Figure 1 An example of an eye with sparse retinal vasculature or below the retinal fractal dimension (D_f) threshold of 1.472 (A) compared to an eye with a more dense retinal vasculature pattern or D_f greater than the 1.472 threshold value (B) in this study.

Table 4 Association between tertiles of retinal geometric measures (D_f, curvature tortuosity, branching angle) and prevalence of heart failure.

Retinal vascular geometric measures	No. of cases/no. at risk	Prevalence of heart failure (n = 62)	
		Model 1 OR (95% CI)[a]	Model 2 OR (95% CI)[b]
Fractal dimension			
1st tertile	26/309	1.44 (0.68-3.05)	1.35 (0.62-2.91)
2nd tertile	24/306	1.60 (0.78-3.31)	1.49 (0.70-3.16)
3rd tertile	12/279	1.0 (reference)	1.0 (reference)
Arteriolar tortuosity			
1st tertile	26/266	1.62 (0.87-3.03)	1.72 (0.87-3.43)
2nd tertile	17/281	1.03 (0.52-2.03)	1.11 (0.53-2.29)
3rd tertile	19/347	1.0 (reference)	1.0 (reference)
Venular tortuosity			
1st tertile	20/284	0.97 (0.50-1.85)	1.06 (0.53-2.12)
2nd tertile	21/271	1.13 (0.60-2.13)	1.16 (0.58-2.31)
3rd tertile	21/339	1.0 (reference)	1.0 (reference)
Arteriolar branching angle			
1st tertile	26/297	1.82 (0.93-3.59)	1.79 (0.86-3.75)
2nd tertile	22/296	1.62 (0.81-3.24)	1.77 (0.85-3.70)
3rd tertile	14/301	1.0 (reference)	1.0 (reference)
Venular branching angle			
1st tertile	28/290	1.79 (0.97-3.30)	1.73 (0.90-3.34)
2nd tertile	15/295	0.87 (0.43-1.75)	0.91 (0.44-1.89)
3rd tertile	19/309	1.0 (reference)	1.0 (reference)

Abbreviations: OR, odds ratio; CI, confidence intervals.

[a]Adjusted for age and sex.

[b]Further adjusted for ethnicity, systolic blood pressure, body mass index, and presence of type 2 diabetes.

selectin, was shown to be present in patients with AF [23]. Moreover, suboptimal retinal vasculature may also be due to systemic inflammation and endothelial dysfunction [18,24]. Griffith et al. [25] have shown that the endothelium has a key role in optimisation of vascular geometry, by nitric oxide (NO) and endothelin-1 release; hence, alteration from vascular network optimality may reflect endothelial dysfunction.

In addition, altered optimal retinal vessel geometry is associated with altered shear stress across this network, which may further compound the effects on the vascular endothelium [26] and result in endothelial inflammation via increased expression of pro-inflammatory genes [27,28], greater production of superoxide and hydrogen peroxide free radicals [28], and decreased levels of important intracellular antioxidants [24,29]. Therefore, we speculate that the observed association between a lower D_f and prevalence of AF in our study could be mediated by pathways involving inflammation and/or endothelial dysfunction.

The mechanisms underlying differences in geometric parameters (i.e. reduced fractal dimensions) and their clinical significance are unclear [30]. Nevertheless, our findings suggest that fractal analysis in particular could be a potentially useful non-invasive tool for early risk stratification in AF. Fractal analysis of the retinal vasculature has previously demonstrated a high level of reproducibility by our group [31]; however, the time to process each image needs to be shortened before its clinical utility needs to be considered [32]. Nevertheless, given that retinal vascular fractals predict long-term microvascular complications [32], it seems plausible that subtle changes in the retinal branching network may be an early indicator of future disease [33] such as AF.

The strengths of this study include its relatively large sample size, the use of quantitative methods for assessing retinal vascular geometric measures by standardised protocols; and the collection of information on important confounders. However, the current study has some noteworthy limitations. First, the cross-sectional study design precludes the inference of any causal effects. Second, there are limitations to the measurement of D_f based on binary vessel images, whether calculated based on the box-counting method as in the present study, or other alternative methods such as the information dimension and the correlation dimension [34]. The reliability of D_f is uncertain, with data suggesting that the relative standard deviation of D_f is greater than the relative errors among clinical subjects [34]. Third, diastolic and systolic blood pressure and heart rate were measured with only a single reading, which is not in line with the current recommendations for blood pressure measurement. Hence, this is likely to undermine the reliability of the blood pressure data in our study. Finally, the study population is comprised of patients who underwent angiography for potential coronary artery disease at a tertiary hospital centre. As such, the population was not randomly selected, and consisted of a higher proportion of hyperlipidaemic, diabetic and hypertensive male populations [6]. Therefore, our findings might not be generalisable to other population subsets such as younger, healthy females.

In summary, we show for the first time that reduced fractal dimension reflecting a sparser branching pattern and lower vascular structural complexity, was independently associated with greater odds of having AF. Additional prospective studies that are adequately powered are needed to investigate whether temporal changes to the retinal vascular geometry are predictive of AF and heart failure in the longer term.

Conflicts of Interest

The authors report no relationships that could be construed as a conflict of interest.

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