Fractal analysis of retinal microvasculature and coronary heart disease mortality

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Aim

Fractal analysis provides a global assessment of vascular network architecture. We examined the relationship of retinal vascular fractal dimension ($D_f$) with coronary heart disease (CHD) mortality.

Methods and results

We examined the relationship of $D_f$ with 14-year CHD mortality in a prospective, population-based cohort of 3303 participants aged 49 years or older. $D_f$ was measured from digitized fundus photographs using computer-automated methods; CHD mortality was documented from Australian National Death Index records. Mean $D_f$ in this population was 1.441 (standard deviation, 0.024). Over 14 years, there were 468 (14.2%) CHD deaths. Participants with suboptimal $D_f$ (lowest and highest quartiles) had 50% higher 14-year CHD mortality than those with optimal $D_f$ (middle quartiles), after adjusting for age, blood pressure, and other risk factors. Among participants aged ≤ 70 years, suboptimal $D_f$ was associated with a nearly two-fold higher risk of CHD mortality [adjusted hazard ratio (HR) 1.89, 95% confidence interval (CI), 1.25, 2.84 for the lowest quartile and HR 1.87, CI 1.30, 2.69 for the highest quartile, compared with middle quartiles].

Conclusions

$D_f$ is a novel means of quantifying microvascular branching that independently predicted 14-year CHD mortality. These findings suggest that suboptimal microvascular branching may play a role in development of clinical cardiovascular disease.

Keywords

Microcirculation • Coronary heart disease • Mortality • Fractals • Retinal microcirculation • Blue Mountains Eye Study

Introduction

Coronary heart disease (CHD) is the leading cause of death worldwide. While the majority of CHD is attributable to coronary artery disease in the epicardial coronary arteries, there is increasing recognition that coronary microvascular disease also plays an important role, particularly in women, and in those with diabetes.1 However, directly probing the coronary microcirculation is difficult, and surrogate microvascular beds such as the retinal vascular network have been used to non-invasively study the health of the systemic microcirculation.2,3 Most research to date has focused on changes in the calibre of retinal vessels, which are now known to independently predict risk of CHD in women.4–6 but this approach is limited as it measures only a single aspect of vascular structure (calibre) and disregards information in branching patterns and density.

Fractal analysis provides a global assessment of the architecture of a vascular network,2,3 particularly the branching and density of small vessels. It has been applied in diverse areas of vascular medicine to describe complex bifurcating biological structures7 such as the branching patterns of retinal,8,9 coronary,10 and pulmonary arterioles,11 as well as complex biological rhythms such as cardiac arrhythmias12–14. The retinal vasculature can be considered a fractal as it is a geometric pattern whose ‘parts resemble the whole’ (i.e. the property of self-similarity),15,16 and is quantified in terms of the fractal dimension.

Retinal fractal analysis has recently been applied to study the contribution of microvascular network structure to chronic
Fractals and CHD

Methods

Study population
We examined the relationship of \(D_f\) and CHD mortality in the Blue Mountains Eye Study, a prospective, population-based cohort of predominantly Caucasian people aged 49 years or older at the study commencement in 1992. Baseline participants \(n = 3654\) represented 82.4% of eligible potential participants living in two postcode areas in the Blue Mountains region, New South Wales, Australia, and now have completed follow-up data over 14 years. This study was conducted according to the recommendations of the Declaration of Helsinki, and was approved by the Western Sydney Area Health Service Human Research Ethics Committee and the University of Sydney Human Research Ethics Committee. Written, informed consent was obtained from all participants. We excluded 307 participants with poor-quality photographs unsuitable for measuring \(D_f\) and 44 whose cause of death was unclear, leaving 3303 participants (90.4%) who comprised the study population.

Retinal photography and measurement of \(D_f\)
At the baseline examination, 30\(^{1}\) retinal photographs of the optic disc, macula, and other retinal fields of both eyes were taken after pupil dilation using a Zeiss FF3 fundus camera (Carl Zeiss, Oberkochen, Germany). Disc-centred photographs were then digitized and used to measure two parameters: fractal dimension of the retinal vasculature and retinal vessel calibre. Measurement was performed by trained graders masked to participant details.

The programme to measure fractal dimension, International Retinal Imaging Software—Fractal (IRIS—FRACTAL), is described elsewhere.\(^{21}\) Briefly, digital monochrome optic disc-centred images of the right retina were viewed on two 17-inch monitors allowing image displays at 1280 \(\times\) 1024 resolution. Trained graders examined the images, determined the radius of the optic disc and cropped a circular area of 3.5 optic disc radii, centred on the optic disc. Cropping a consistently defined area provides comparable measures among different images of the same individual taken at different time points, or among dissimilar individuals. IRIS—FRACTAL then automatically generates a skeletonized line tracing of the retinal vessels from the image (Figure 1) which the grader examined and compared with the original cropped image to identify and erase artefacts occasionally erroneously included in the tracing such as alpha peripapillary atrophy, choroidal vessels, or pigment abnormalities. \(D_f\) is then calculated from the refined skeletonized line tracing using the box-counting method,\(^{16,22}\) an established method of measuring fractal dimension of structures that are not perfectly self-similar, such as the real-life retinal vasculature.\(^{16,22}\) All measurements were performed by a single grader with high intrgrader reliability (intraclass correlation coefficient 0.95).\(^{21}\) To summarize, the essential elements of measuring fractal dimension involve breaking up the pattern of retinal vessels into short segments (‘skeletonisation’), dividing the entire field into squares (‘boxes’) of a certain size, and counting the number of boxes containing a vessel segment. The process is repeated for boxes of different sizes, the logarithm of the number of boxes containing a segment is plotted against the logarithm of the number of boxes covering the image, and the fractal dimension is calculated from the slope, by the computer program.

Retinal arteriolar and venular calibres were also measured from photographs using a separate computer program (IVAN, University of Wisconsin), described elsewhere.\(^{5,23,24}\) Individual vessel calibre measurements were combined into summary indices, referred to as central retinal artery equivalent and central retinal vein equivalent, which represent the estimated mean retinal arteriolar and venular calibre, respectively. As previously reported, intra- and inter-grader grading agreement was high, with quadratic weighted \(\kappa\) values ranging from 0.80 to 0.93.\(^{23,25}\) Further details are given elsewhere.\(^{23,25}\)

Measurement of other variables
Resting systolic and diastolic blood pressure (BP) measurements were taken using the same mercury sphygmomanometer with appropriate adult cuff size after participants had been seated for at least 10 min. We adapted the 2003 World Health Organization (WHO) guidelines defining hypertension, taking as hypertensive grade 2 or above (severe...
hypertension), for those persons previously diagnosed as hypertensive and currently using anti-hypertensive medications, or those with a systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg at examination.\textsuperscript{5,23} We defined diabetes as a physician diagnosis of diabetes, or fasting blood sugar ≥ 7 mmol/L. Serum total cholesterol and high-density lipoprotein (HDL) cholesterol were measured from fasting blood specimens using standard procedures.\textsuperscript{5,23} White blood cell count was determined using Coulter counter methods. We obtained self-reported history of angina and acute myocardial infarction from face-to-face interviews and defined history of CHD if either of these conditions was present. These definitions are described in detail elsewhere.\textsuperscript{5,23}

**Assessment of coronary heart disease mortality**

Coronary heart disease mortality was based on deaths and causes of death from the Australian National Death Index (NDI).\textsuperscript{5,23} Causes of death in the NDI database are collected from death certificates, which are completed by the physician in attendance, coroner, or medical examiner, regardless of whether the death occurred in a hospital or in the community, and recorded using International Classification of Diseases (ICD) codes. A CHD death was defined if any of the following codes from ICD-9 was included in the causes of death (410.0–9, 411.0–8, 412, 414.0–9) and ICD-10 (I21.0–9, I22.0–9, I23.0–8, I24.0–9, I25.0–9).\textsuperscript{5} The validity of Australian NDI data is reported to have high sensitivity and specificity for cardiovascular mortality (92.5 and 89.6%, respectively).\textsuperscript{26} The census cut-off for CHD death was 31 December 2005 (14-year follow-up).

**Statistical analysis**

We examined 14-year age–gender-adjusted survival curves by quartile of $D_f$, with the 1st quartile representing those with the lowest $D_f$ values. We used Cox regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of CHD mortality in different quartiles. Multivariable models adjusting for age, gender, and other variables including retinal arteriolar and venular calibre were constructed. We previously reported from this cohort that retinal vascular calibre was associated with incident CHD in persons aged ≤ 70.\textsuperscript{5} We thus performed subgroup analyses by age, as well by gender, hypertension and diabetes status.

We used two methods to test proportional hazards assumptions with respect to the time period variable, namely visual inspection of the log cumulative hazard plots and adding time-dependent variables into the first multivariable model. Age violated the proportional hazards assumption and hence was modelled as a strata variable (in 10-year categories). SAS v9.12 was used for analyses. Two-sided tests were used and $P$-value < 0.05 was used as the threshold for significance. To compare the baseline characteristics across four quartiles, we used GLM (analysis of covariance). $P$ for trend was calculated by using the median of corresponding quartile as the independent variable.

**Role of the funding source**

The funding source had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

**Results**

Mean $D_f$ in this population of 3303 older adults was 1.441, with standard deviation (SD) of 0.024. Over the follow-up period of 14 years, 468 participants (14.2%) died of CHD causes. The mean $D_f$ was 1.434 in persons who died from CHD and 1.442 in those who either survived or died from causes other than CHD. As the first visit was between 1992 and 1994 and the cut-off census date was 31 December 2005 for everyone, the follow-up time varied slightly between individuals, with mean follow-up of 13.1 years (SD = 0.5 years, median = 13.1 years, inter-quartile range 12.6–13.6 years, minimum = 12.0 years, maximum = 14.0 years).

Table 1 shows the baseline characteristics of the cohort. Suboptimal $D_f$ (either highest or lowest quartiles) was associated with different cardiovascular risk factors (Table 1). Increasing age, higher BP, higher fasting glucose, and higher plasma fibrinogen were associated with lower (‘sparser’) $D_f$. Male gender, higher body mass index (BMI), dyslipidaemia (lower HDL cholesterol, higher triglycerides), and smoking were associated with higher (‘denser’) $D_f$. In preliminary analysis of age–gender-adjusted survival curves for the cohort, a U-shaped relationship of $D_f$ with CHD mortality was evident, where sub-optimal $D_f$ (lowest and highest quartiles) was associated with the highest risk (Figure 2, see Figure 1 for examples of eyes with low and high $D_f$). Subsequent analyses thus examined risk in the two extreme quartiles (1st and 4th) compared with the middle quartiles (2nd and 3rd).

Table 2 shows that participants with the lowest $D_f$ quartiles had a 44% higher risk of CHD mortality, while those with the highest $D_f$ quartiles had a 51% higher risk, after multivariate adjustment for risk factors. These associations did not alter substantially after further adjustment for retinal arteriolar and venular calibre (Table 2).

Age had a significant effect on modifying the relationship of $D_f$ with CHD mortality. \(P\) interaction = 0.06 for low and 0.03 for high $D_f$). In persons younger than our a priori age cut-off ≤ 70 years at baseline, the relationship strengthened, with suboptimal $D_f$ in both the lowest and highest quartiles, respectively, associated with an almost two-fold higher risk of CHD mortality (adjusted HR 1.89, 95% CI 1.25, 2.84 and HR 1.87, CI 1.30, 2.69, respectively, Table 3). Among persons older than 70 years at baseline, the association of suboptimal $D_f$ with CHD mortality was considerably weaker and was not statistically significant (adjusted HR for the lowest and highest quartiles, 1.21, CI 0.90, 1.64 and HR 1.13, CI 0.72, 1.78, respectively, Table 3). Using other age cut-offs (e.g. 65, 75 years) showed a similar finding of stronger associations in younger age groups (data not shown).

The findings were also similar in persons with and without hypertension, and in those with and without diabetes, with no evidence of interaction with these risk factors (data not shown). The association of suboptimal $D_f$ with CHD mortality was slightly stronger in women than in men, although the gender interaction was not statistically significant. The adjusted HR was 1.71, CI 1.19, 2.45 and HR 1.47 CI 0.93, 2.30 for the lowest and highest quartiles in women, respectively. Corresponding values in men were HR 1.26, CI 0.90, 1.78 and HR 1.55 CI 1.09, 2.20, respectively (data not shown).

**Discussion**

The human circulatory system conforms to optimal design principles (Murray principle of minimum work) and deviations
Table 1  Characteristics of participants in the Blue Mountains Eye Study cohort (n = 3303), by fractal dimension ($D_f$)

<table>
<thead>
<tr>
<th>Quartiles of $D_f$</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>$P$ for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean $D_f$ (SD)</td>
<td>1.408 (0.018)</td>
<td>1.437 (0.005)</td>
<td>1.450 (0.004)</td>
<td>1.467 (0.008)</td>
<td></td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>71.2 (9.6)</td>
<td>66.0 (8.7)</td>
<td>64.0 (8.4)</td>
<td>61.3 (7.9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>39.7</td>
<td>41.9</td>
<td>46.9</td>
<td>46.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean systolic BP, mmHg (SD)</td>
<td>152 (23)</td>
<td>146 (21)</td>
<td>145 (20)</td>
<td>140 (19)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mean diastolic BP, mmHg (SD)</td>
<td>84 (11)</td>
<td>84 (10)</td>
<td>84 (10)</td>
<td>83 (10)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean arterial BP, mmHg (SD)</td>
<td>106 (13)</td>
<td>104 (12)</td>
<td>104 (12)</td>
<td>102 (12)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m² (SD)</td>
<td>25.6 (4.5)</td>
<td>26.0 (4.4)</td>
<td>26.6 (4.8)</td>
<td>26.4 (4.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Plasma HDL cholesterol, mmol/L (SD)</td>
<td>1.46 (0.43)</td>
<td>1.46 (0.45)</td>
<td>1.41 (0.43)</td>
<td>1.40 (0.45)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Triglycerides, mmol/L (SD)</td>
<td>5.4 (1.9)</td>
<td>5.2 (1.2)</td>
<td>5.2 (1.7)</td>
<td>5.2 (1.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L (SD)</td>
<td>6.4 (1.7)</td>
<td>6.6 (1.8)</td>
<td>6.5 (1.6)</td>
<td>6.5 (1.8)</td>
<td>0.61</td>
</tr>
<tr>
<td>White cell count, $\times 10^3$ (SD)</td>
<td>4.3 (1.1)</td>
<td>4.1 (1.5)</td>
<td>3.9 (1.0)</td>
<td>4.0 (1.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Plasma fibrinogen, mmol/L (SD)</td>
<td>79.6</td>
<td>72.4</td>
<td>69.3</td>
<td>61.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypertensive (%)</td>
<td>10.9</td>
<td>15.2</td>
<td>14.3</td>
<td>20.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>18.3</td>
<td>18.3</td>
<td>14.6</td>
<td>15.7</td>
<td>0.20</td>
</tr>
<tr>
<td>History of CHD (%)</td>
<td>18.3</td>
<td>14.1</td>
<td>14.6</td>
<td>15.7</td>
<td>0.20</td>
</tr>
<tr>
<td>Mean retinal arteriolar calibre, $\mu$m (SD)</td>
<td>219 (21)</td>
<td>224 (20)</td>
<td>227 (19)</td>
<td>231 (20)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

SD refers to standard deviation; BP to blood pressure; HDL to high-density lipoprotein; CHD to coronary heart disease.

Figure 2 Fractal dimension ($D_f$) and 14-year coronary heart disease mortality (adjusted for age and gender).
from optimal architecture are postulated to result in impaired microcirculatory transport, reduced efficiency and thereby, a greater risk of clinical cardiovascular disease. For example, the particular angles at which coronary and cerebral arteries branch, and the relationship of parent and daughter arterial diameters at bifurcations, serve to optimize blood transport. Inefficient or suboptimal microvascular architecture (e.g., microvascular branching density that is too sparse or too dense) is thought to increase energy costs and reduce the efficiency of metabolic transport and thus increase cardiovascular risk.

The retinal vascular fractal dimension, \( D_f \), is a global measure of microvascular architecture and complexity. Fractal dimension can be conceived as the amount of space or density that a particular object occupies. A line has fractal dimension of 1, while a square or circle, by filling up 2 dimensions, has a fractal dimension of 2. A branching structure has a fractal dimension between 1 and 2. A sense of the different patterns of space filling quantified by \( D_f \) can be seen in Figure 1. Participants with suboptimally low or high \( D_f \) experienced a 50% greater risk of CHD mortality, after adjusting for the effects of age, gender, BP, and other cardiovascular risk factors. This relationship was stronger in younger participants (baseline ages \( \leq 70 \) years), in whom suboptimal \( D_f \) predicted an almost two-fold higher risk of CHD mortality.

Our results provide new data on the relationship between geometric complexity and optimality of vascular networks and the risk of CHD. There are few studies for direct comparison. In type 1 diabetics, higher retinal \( D_f \) has been found to be directly related to risk of diabetic retinopathy although another study found lower \( D_f \) associated with increased risk of proliferative retinopathy and nephropathy. We previously examined a subsample of the current population and showed that reduced \( D_f \) was associated with higher systolic BP and hypertension. In contrast, another study that recruited 40 participants with acute stroke reported no \( D_f \) difference between participants with and without hypertension. This second study was acknowledged, however, to have insufficient power to detect small differences in \( D_f \). Our findings are consistent with a recent report of a similar U-shaped relationship of suboptimal \( D_f \) with CKD, which may be attributed to increased tissue stress from impaired flow. A U-shaped relationship of \( D_f \) and certain stroke subtypes may also apply, as one study reported low \( D_f \) associated with lacunar stroke while another reported an association with high \( D_f \). Case-control studies that find geometric parameters of the retinal vasculature such as branching angles of human retinal vessels and the number of bifurcations, are associated with risk of CHD, stroke and peripheral arterial disease also support our results.

### Table 2 Fractal dimension (\( D_f \)) and 14-year coronary heart disease mortality

<table>
<thead>
<tr>
<th>Quartiles of ( D_f )</th>
<th>CHD Mortality</th>
<th>Age (&lt; 70) years</th>
<th>( % (n) )</th>
<th>Multivariate-adjusted HR(^*) (95% CI) P-value</th>
<th>( % (n) )</th>
<th>Multivariate-adjusted HR(^*) (95% CI) P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st (lowest, 1.323–1.427)</td>
<td>22.0 (180)</td>
<td>1.39 (1.12, 1.72) 0.003</td>
<td>1.44 (1.13, 1.83) 0.004</td>
<td>1.51 (1.17, 1.94) 0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd and 3rd (middle, 1.428–1.457)</td>
<td>11.5 (190)</td>
<td>1.0 (reference) –</td>
<td>1.0 (reference) –</td>
<td>1.0 (reference) –</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4th (highest, 1.458–1.506)</td>
<td>11.9 (98)</td>
<td>1.55 (1.21, 1.99) 0.0005</td>
<td>1.51 (1.14, 1.98) 0.004</td>
<td>1.58 (1.19, 2.10) 0.002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR refers to hazard ratio; CI to confidence interval.

\(^*\)Multivariate analyses adjusted for age, sex, body mass index, mean arterial blood pressure, smoking history, diabetes, history of CHD, white cell count, plasma fibrinogen, triglycerides, and high-density cholesterol.

### Table 3 Fractal dimension (\( D_f \)) and 14-year coronary heart disease mortality, stratified by baseline age

<table>
<thead>
<tr>
<th>Quartiles of ( D_f )</th>
<th>CHD Mortality</th>
<th>Age ( \leq 70) years</th>
<th>( % (n) )</th>
<th>Multivariate-adjusted HR(^*) (95% CI) P-value</th>
<th>Age ( &gt; 70) years</th>
<th>( % (n) )</th>
<th>Multivariate-adjusted HR(^*) (95% CI) P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st (lowest)</td>
<td>11.2 (41)</td>
<td>1.89 (1.25, 2.84)</td>
<td>0.002</td>
<td>30.6 (139)</td>
<td>1.21 (0.90, 1.64)</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>2nd and 3rd</td>
<td>7.0 (86)</td>
<td>1.0 (reference) –</td>
<td>–</td>
<td>24.5 (104)</td>
<td>1.0 (reference) –</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>4th (highest)</td>
<td>8.6 (61)</td>
<td>1.87 (1.30, 2.69) 0.0008</td>
<td>32.2 (37)</td>
<td>1.13 (0.72, 1.78)</td>
<td>0.60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR refers to hazard ratio; CI to confidence interval. The P-value for age interaction = 0.06 for low and 0.03 for high \( D_f \).

\(^*\)Multivariate analyses adjusted for age, sex, body mass index, mean arterial blood pressure, smoking history, diabetes, history of CHD, white cell count, plasma fibrinogen, triglycerides, and high-density cholesterol.
The pathological processes that underlie variations in $D_f$ are not well understood. In our study, all major cardiovascular risk factors were associated with sub-optimal fractals (either reduced or increased $D_f$). We suggest that lower $D_f$ may result from a range of cardiovascular processes that include older age and higher levels of BP, fasting glucose, and plasma fibrinogen (a marker of systemic inflammation), all of which were associated with low $D_f$ in our population (Table 1). Other studies have also documented an association of lower $D_f$ with aging and these associations are consistent with clinical observations that lower $D_f$ represents a loss of branches or rarefaction of the microcirculation in older individuals, and in those with hypertension and other vascular diseases. Rarefaction of circulation may predispose to CHD through a reduced ability to form collaterals after ischaemic events. In contrast, a different spectrum of cardiovascular risk factors including male gender, higher BMI, dyslipidaemia (either lower HDL cholesterol or higher triglyceride levels), and smoking were associated with higher $D_f$ or increased density or branching of the microcirculation. Higher $D_f$ may be a marker of ischaemia, as it also occurs in diabetic retinopathy and anterior ischaemic optic neuropathy (vascular ischaemia of the optic nerve head). Changes in $D_f$ may be mediated by the vascular endothelium as it plays a major role in maintaining optimality at vascular branches.

Our group and others previously showed that retinal vascular calibres (either narrower retinal arterioles or wider retinal venules) are also early markers of microvascular disease that independently predict cardiovascular disease and cardiac function. Even after adjusting for retinal vascular calibre, the association of suboptimal $D_f$ with CHD mortality remained strong, indicating that $D_f$ conveys additional prognostic information. Taken together, these results suggest that microvascular health is maintained by both adequate vascular calibres and optimal branching architecture. The same association was observed in persons with and without hypertension, further supporting an independent relationship of suboptimal $D_f$ to CHD mortality that is not mediated through the effects of hypertension.

The stronger association of suboptimal $D_f$ and CHD mortality in younger, middle-aged people is consistent with the known relationship of retinal vascular changes to CHD, and the general epidemiology of cardiovascular risk factors. For example, the increased risk of vascular mortality with elevated BP appears to be greater in younger people. Weaker associations in persons older than 70 years at baseline could be due to a greater contribution from large vessel atherosclerosis, although even in this group a weak U-shaped relationship was present (Table 3).

Our results have several implications. First, they demonstrate the feasibility of using fractal analysis to study microvascular branching architecture. The ability to quantify microcirculatory branching may suggest new avenues of research in both clinical and laboratory studies of haemodynamics, angiogenesis, and pharmacology. Second, they demonstrate that microvascular health is influenced by vascular branching architecture as well as vascular calibres, with implications for assessing new pharmacological therapies targeted at microvasculature. Third, our findings raise the possibility of non-linear relationships between microvascular dysfunction and CHD, as predicted by bifurcation models, although this clearly needs confirmation in further studies. Non-linear relationships with some cardiovascular risk factors, such as BMI have been reported. Fourth, we speculate that $D_f$ as a novel marker of suboptimal vascular branching may potentially be useful in screening and/or diagnosing coronary microvascular dysfunction non-invasively, or in monitoring disease progression and response to therapy. The ready availability of (non-mydriatic) digital retinal photography, minimal manual input, and rapid computer-automated image analysis makes this an attractive biomarker for further study.

Our study has several strengths including its prospective design with long follow-up of a moderately large cohort, masked, objective measurement of $D_f$ with minimal manual grading input and the assessment of CHD mortality from validated death records. The following limitations deserve mention. First, we measured $D_f$ in the retinal microcirculation rather than the coronary microcirculation and assumed that changes in architecture in the former mirror similar changes in the latter. This may be a reasonable assumption as coronary microvascular disease may be part of a systemic microvascular disorder. Nonetheless, the coronary circulation is a three-dimensional network, whereas the retinal network is two-dimensional. This simplifies the fractal analysis but the correspondence between fractal changes in both networks is currently unclear. Future research investigating how retinal vascular fractal changes (measured using our program or similar techniques) correlate with organ vascular fractal changes (measured using techniques such as CT angiography) are needed. Second, although we demonstrate a link between suboptimal microvascular branching and CHD mortality, the mechanism underlying these observations is unclear. We speculate that this is related to inefficient transport which, through the Murray principle of minimum work, results in cardiovascular disease. More definitive evidence demonstrating inefficient flow and increased ischaemia in the presence of suboptimal $D_f$ should be obtained from animal or human tissue models, as well as longitudinal studies. Our study, using data from photographs collected in 1992–94, did not measure functional characteristics of the retinal microvasculature. Such measures would provide greater insight into the inter-relationship of vascular morphology and function and clinical cardiovascular events. It is likely that vasoactive substances influence both vascular function and morphology, and interact to cause clinical disease. Few studies have examined this aspect. One study in patients with brain tumours found a direct correlation of in vivo metabolism with histological cerebral tissue fractal dimension, illustrating the close link between branching and metabolism. Other studies have shown that changes in retinal vascular calibre, a feature highly correlated with retinal fractals, are associated with brachial flow-mediated vasodilation and impaired flicker-induced retinal vasodilatory response, both measures of nitric oxide processes and thus endothelial function. Retinal arteriolar calibre is also associated with measures of myocardial blood flow and perfusion in asymptomatic patients with no evidence of coronary atherosclerosis. Further research combining both morphological and functional assessment of the retinal vasculature would be informative. Finally, although we collected information on and controlled for important confounders, other unmeasured factors (e.g. use of vasodilator drugs and...
other subclinical vascular co-morbidities) could have affected or confounded the study associations.

In summary, we show that persons with suboptimal retinal vascular branching (either low or high values of $D$, representing sparser or denser branching patterns, respectively) have higher CHD mortality when compared with persons with values around the population mean. This increased risk is independent of age, gender, smoking, BP, and other risk factors. Our results highlight the role that microvascular branching patterns may play in developing cardiovascular disease. Further research into the role of microvascular branching and transport efficiency in maintaining healthy vascular systems may provide novel understanding of the genesis of cardiovascular disease as well as potential new targets for diagnosis, prevention and treatment.

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References

Pneumomediastinum after implantable cardiac defibrillator implantation

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A 66-year-old male with prior tuberculosis pleuritis and anterior myocardial infarction was admitted to our hospital for sustained polymorphic ventricular tachycardia. The patient was already on oral amiodarone, sotalol, and perindopril. Invasive external overdrive pacing terminated the arrhythmia. Acute ischaemia was ruled out and an implantable cardiac defibrillator (ICD) implantation was decided. A Medtronic-6931 defibrillator lead was placed in the right ventricle and a Medtronic-5076 lead was easily placed in the right atrial appendage. Both leads were inserted via the left cephalic vein and connected to a Medtronic INTRINSIC-7288 ICD implanted in the prepectoral area. Normal sensing and capture were obtained.

The day after implantation, the patient complained of chest pain increased by deep breathing. Clinical examination and chest X-ray were unremarkable. Echocardiography showed no pericardial effusion. The next day, chest X-ray showed a right partial pneumothorax (Panel A). Atrial pacing threshold had dramatically increased (>6 V) and P-wave sensing was poor (0.3 mV). In addition to pneumothorax, thoracic computed tomography (CT) showed pneumopericardium and pneumomediastinum (Panels B and C, black arrows), likely due to an atrial lead pleuropéricardial perforation. A slight extrusion of the atrial lead through the atrium was identified (Panel D, white arrow). The atrial lead was extracted in emergency under general anaesthesia. The procedure was uncomplicated. The CT performed 5 days later found no residual pneumopericardium or pneumomediastinum. A 3-year follow-up revealed no complications.

This case reminds us that severe mechanical complications can occur after pacemaker or ICD implantation, especially in patients with lung disease history. With this regard, CT is of particular interest in the early post-procedure period.

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