CARDIOVASCULAR MEDICINE

Retinal vascular calibre and the risk of coronary heart disease-related death

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Objective: To examine whether retinal vascular calibre independently predicts risk of coronary heart disease (CHD) -related death.
Methods: In a population-based cohort study of 3654 Australians aged ⩾ 49 years, retinal arteriolar and venular calibres were measured from baseline retinal photographs and the arteriole to venule ratio (AVR) was calculated. CHD-related death was confirmed from the Australian National Death Index.
Results: Over nine years, 78 women (4.1%) and 114 men (7.8%) had incident CHD-related deaths. In people aged 49–75 years, wider venules were associated with CHD death, with relative risk (RR) 1.8 (95% confidence interval (CI) 1.1 to 2.7) and RR 2.0 (95% CI 1.1 to 3.6) per standard deviation (SD) increase in venular calibre for men and women, respectively, after adjustment for traditional risk factors. Additionally, in women aged 49–75 years, smaller AVR and narrower arterioles were associated with CHD death (RR 1.5, 95% CI 1.1 to 2.2, and RR 1.9, 95% CI 1.0 to 3.5 per SD decrease in AVR and arteriolar calibre, respectively, after adjustment). These associations were not observed in people aged > 75 years.
Conclusions: These findings suggest that microvascular disease processes may have a role in CHD development in middle-aged people, particularly in women. Retinal photography may be useful in cardiovascular risk prediction.

A recent editorial by Cordero in this journal highlighted several aspects of coronary heart disease (CHD) that differ in women and men.[1] As compared with men, women experience excess risk from hypertension, diabetes, systemic inflammation and hypertriglyceridaemia.[2–5] This sex difference in CHD risk has been reported to be more pronounced in younger people.[6–10] Reasons for this sex difference are unclear, but a possible explanation is that microvascular disease may have a greater role in CHD pathogenesis in women than in men.[11–13]

The retinal microvasculature offers an easily accessible site for non-invasive evaluation of the condition of the microcirculation. Some studies have documented the relationship between retinal arteriolar changes and CHD,[14–17] several of which reported a stronger link in women than in men.[16 17] For example, the ARIC (Atherosclerosis Risk In Communities) study recently reported that a smaller arteriole to venule ratio (AVR; the ratio of the calibre of retinal arterioles to that of venules) was associated with higher risk of incident CHD death in women but not in men.[17] On the basis of these findings, the WISE (Women's Ischemia Syndrome Evaluation) study included retinal photography as a component of its evaluation of women at risk of myocardial ischaemia and CHD.[18] Other authors have stressed the need to confirm these findings in other populations.[19 20] Moreover, it is not known whether lower AVR represents narrower arterioles or wider venules, or both.

In the current study, we examined the relationship between retinal vascular calibre and CHD death in a population-based cohort of women and men aged 49 years or older. Our objectives were to assess (1) in which age and sex subgroups, if any, retinal vascular calibre is associated with CHD death; and (2) whether variations in arteriolar or venular calibre are responsible for these associations.

PATIENTS AND METHODS

The Blue Mountains Eye Study is a population-based cohort of predominantly Caucasian people aged 49 years or older at the start of the study in 1992. Baseline participants (n = 3654) were 82.4% of eligible potential participants living in two postcode areas in the Blue Mountains, New South Wales, Australia. This study was conducted according to the recommendations of the Declaration of Helsinki and was approved by the Western Sydney Area Human Research Ethics Committee and the University of Sydney Human Research Ethics committee. Written, informed consent was obtained from all participants. The study population comprised 3340 participants who had baseline retinal photographs gradable for retinal vessel calibre.

At the baseline examination (1992–4), stereoscopic retinal photographs (30°) of the macula and other retinal fields of both eyes, by using a Zeiss FF3 fundus camera (Carl Zeiss, Oberkochen, Germany), were taken after pupil dilatation. Detailed grading methods were described previously[21] and are identical to the methods used in the ARIC study.[17] In brief, we used a computer-assisted method to measure the internal calibre of retinal arterioles and venules from all gradable digitised retinal images, which were then summarised by formulas by Parr and Hubbard,[22 23] with correction for magnification.[24 25] The formulas take into account branching patterns and allow all measured vessel calibres in an eye to be summarised as an index representing the mean arteriolar or venular calibre of that eye. AVR is calculated from these indices. An AVR of 1.0 suggests that arteriolar calibres are, on average, the same as venular calibres in that eye, and a lower AVR suggests either relatively narrower arterioles than venules or relatively wider venules than arterioles. As previously reported, intragrader and intergrader grading agreement is high, with quadratic weighted κ values ranging from 0.80 to 0.93.[23]

Abbreviations: ARIC, Atherosclerosis Risk In Communities; AVR, arteriole to venule ratio; CHD, coronary heart disease; HDL, high density lipoprotein; ICD, *International Classification of Diseases*; NDI, National Death Index; RR, relative risk; WISE, Women's Ischemia Syndrome Evaluation

At baseline, we measured participants' height, weight and blood pressure. We measured the systolic and diastolic blood pressure of each participant once with a single mercury sphygmomanometer with appropriate adult cuff size, after seating the participant for at least 10 min. Diabetes was defined as a physician's diagnosis of diabetes or a fasting blood glucose ⩾ 7 mmol/l. Body mass index was calculated from height and weight. Pre-existing CHD was defined as a self-reported history of CHD (angina or acute myocardial infarction) at baseline. We adapted the 2003 World Health Organization/International Society of Hypertension guidelines to define hypertension,[26] taking as severe hypertension (grade 2 or above) if the participant had a previous diagnosis of hypertension and was taking hypertension drugs at the time of the study or had systolic blood pressure ⩾ 160 mm Hg or diastolic blood pressure ⩾ 100 mm Hg at examination.

Deaths that occurred during the period between the baseline examination and 31 December 2001 were confirmed by matching the demographic information of the 3654 participants with Australian National Death Index (NDI) data, by using probabilistic record linkage.[27 28] The sensitivity and specificity of Australian NDI data have been estimated to be 93.7% and 100% for all deaths, and 92.5% and 89.6% for cardiovascular deaths.[27 28] Cause of death was provided by the NDI, which records cause of death as documented on death certificates, and defined according to the *International Classification of Diseases* (ICD) 9th and 10th revisions. CHD deaths were defined according to codes 410.0–9, 411.0–8, 412 and 414.0–9 (from ICD-9) and I21.0–9, I22.0–9, I23.0–8, I24.0–9 and I25.0–9 (ICD-10).

SAS (SAS Institute, Cary, North Carolina, USA) was used for statistical analysis. CHD mortality was calculated as the number of CHD deaths/1000 person years of follow up. We modelled AVR and arteriolar and venular calibres as continuous variables (per SD). To assess the individual contributions of vessel calibre while avoiding collinearity between arteriolar and venular calibres, we created two new variables of venule-adjusted arteriolar calibre and arteriole-adjusted venular calibre, following the residual method suggested by Willett and Stampfer.[29]

We used Cox regression models to assess the association between AVR, and retinal arteriolar and venular calibres at baseline and the risk of CHD death over nine years. We used sex-specific models for all analyses after assessing statistical interactions between age, sex and retinal vessel calibre estimates. The interaction term between age and venular calibre was significant (p = 0.02). We constructed three different multivariate-adjusted models to assess the relative contributions of AVR and arteriolar and venular calibres. In addition to the covariates' age, pre-existing CHD, systolic blood pressure, diabetes and smoking, model 1 assessed either AVR, arteriolar calibre or venular calibre individually in separate models; model 2 assessed both arteriolar and venular calibre simultaneously in the same model; and model 3 assessed either venule-adjusted arteriolar calibre or arteriole-adjusted venular calibre.

We further stratified men and women into two age groups, ⩽ 75 years and > 75 years, to assess the risk of premature CHD death. Total cholesterol and body mass index were not found to be significantly associated with CHD death in either men or women and thus were not included in the multivariate-adjusted models. Survival time was calculated as days

Table 2 AVR quartiles and CHD deaths, by age and sex

AVR		CHD death		
Quartile	**Range**	**No at risk**	**No of deaths**	**Rate***
Women ⩽75 years				
Largest	0.92–1.19	397	5	1.4
3rd	0.87–0.92	396	5	1.5
2nd	0.81–0.87	397	7	2.0
Smallest	0.61–0.81	375	13	4.0
P value for trend			0.02	
Women >75 years				
Largest	0.92–1.17	76	11	21.1
3rd	0.87–0.92	74	9	17.1
2nd	0.82–0.87	72	9	17.3
Smallest	0.61–0.81	97	19	26.5
P value for trend			0.31	
Men ⩽75 years				
Largest	0.90–1.10	305	5	1.9
3rd	0.85–0.90	305	17	7.5
2nd	0.80–0.85	309	19	7.5
Smallest	0.59–0.80	291	14	5.8
P value for trend			0.06	
Men >75 years				
Largest	0.90–1.10	60	12	36.9
3rd	0.85–0.90	60	10	25.8
2nd	0.80–0.85	55	21	64.6
Smallest	0.63–0.80	71	16	33.6
P value for trend			0.29	

*Rate per 1000 person years of follow up.
AVR, arteriole to venule ratio; CHD coronary heart disease.

Table 1 Baseline characteristics of participants, by narrowest and widest AVR quartiles

	Women			Men		
Characteristic	**Smallest quartile (range 0.61–0.82) (n = 472)**	**Largest quartile (range 0.92–1.19) (n = 473)**	**p Value***	**Smallest quartile (range 0.59–0.80) (n = 362)**	**Largest quartile (range 0.90–1.10) (n = 365)**	**p Value***
Age (years)	67.1 (0.44)	64.5 (0.44)	<0.0001	66.8 (0.48)	64.9 (0.50)	0.006
SBP (mm Hg)	153.3 (1.08)	142.7 (0.95)	<0.0001	148.7 (1.06)	139.6 (1.00)	<0.0001
DBP (mm Hg)	86.5 (0.46)	81.6 (0.43)	<0.0001	86.5 (0.57)	81.3 (0.51)	<0.0001
Total SC (mmol/l)	6.4 (0.05)	6.3 (0.05)	0.42	5.78 (0.06)	5.78 (0.06)	0.97
BMI (kg/m^2)	29.9 (0.24)	26.0 (0.23%)	0.0008	26.7 (0.28)	25.4 (0.22)	<0.0001
Pre-existing CHD	50 (10.6%)	59 (12.5%)	0.37	57 (15.8%)	53 (14.5%)	0.64
Severe hypertension	267 (56.6%)	190 (40.2%)	<0.0001	181 (50.0%)	114 (31.2%)	<0.0001
Smoking			0.21			0.15
Never	275 (58.3%)	298 (63.0%)		117 (32.3%)	131 (35.9%)	
Former	122 (25.9%)	106 (22.4%)		181 (50.0%)	183 (50.1%)	
Current	75 (15.9%)	69 (14.6%)		64 (17.7%)	51 (14.0%)	
Diabetes	28 (5.9%)	28 (5.9%)	0.99	27 (7.5%)	34 (9.3%)	0.37

Data are mean (SE) or number (%).
*p Value for difference between smallest and largest quartiles.
AVR, arteriole to venule ratio; BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; SC, serum cholesterol.

Table 3 Retinal vessel indices and RR of CHD death, by age and sex

Retinal vessel index (per SD change*)	CHD death		RR of CHD death (per SD change)*							
			Age-adjusted		Multivariate-adjusted model 1†		Multivariate-adjusted model 2‡		Multivariate-adjusted model 3§	
	No at risk	No of deaths	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Women ⩽75 years	1565	30								
Arteriolar calibre decrease			1.1	0.7 to 2.0	1.3	0.8 to 2.2	1.9	1.0 to 3.5	1.5	1.1 to 2.2
Venular calibre increase			1.6	0.9 to 2.7	1.5	0.9 to 2.5	2.0	1.1 to 3.6	1.5	1.1 to 2.2
AVR decrease			1.5	1.0 to 2.2	1.5	1.1 to 2.2	NA	NA	NA	NA
Women >75 years	319	48								
Arteriolar calibre decrease			0.9	0.5 to 1.4	0.8	0.5 to 1.3	0.8	0.5 to 1.4	0.9	0.7 to 1.2
Venular calibre increase			1.0	0.7 to 1.6	1.1	0.7 to 1.7	1.0	0.6 to 1.7	1.0	0.7 to 1.4
AVR decrease			1.0	0.7 to 1.2	1.0	0.8 to 1.2	NA	NA	NA	NA
Men ⩽75 years	1210	55								
Arteriolar calibre decrease			0.8	0.5 to 1.1	0.8	0.5 to 1.2	1.0	0.7 to 1.6	1.1	0.8 to 1.4
Venular calibre increase			2.0	1.3 to 2.8	1.8	1.2 to 2.6	1.8	1.1 to 2.7	1.4	1.1 to 1.8
AVR decrease			1.3	1.0 to 1.6	1.2	0.9 to 1.5	NA	NA	NA	NA
Men >75 years	246	59								
Arteriolar calibre decrease			1.0	0.7 to 1.5	1.0	0.7 to 1.5	1.0	0.6 to 1.5	1.0	0.8 to 1.3
Venular calibre increase			0.9	0.6 to 1.3	0.9	0.6 to 1.3	0.9	0.5 to 1.5	0.9	0.7 to 1.3
AVR decrease			1.0	0.8 to 1.2	1.0	0.7 to 1.2	NA	NA	NA	NA

In women, mean (SD) values for arteriole to venule ratio (AVR) and arteriolar and venular calibres are 0.869 (0.079), 191.8 (20.0) μm and 221.3 (20.2) μm, respectively.
In men, mean (SD) values for AVR and arteriolar and venular calibres are 0.850 (0.081), 189.1 (20.8) μm and 222.9 (20.3) μm, respectively.
*Per 1 SD decrease in mean arteriolar calibre and AVR; per 1 SD increase in mean venular calibre.
†Model 1: relative risk (RR) adjusted for age, systolic blood pressure, diabetes and smoking.
‡Model 2: RR adjusted for covariates in model 1 plus arteriolar and venular calibre in the same model.
§Model 3: RR adjusted for covariates in model 1 plus either venule-adjusted arteriolar calibre or arteriole-adjusted venular calibre.
CHD, coronary heart disease; NA, not applicable.

survived since the baseline examination to occurrence of CHD death. Relative risk (RR; hazard risk) ratios and 95% confidence intervals (CI) are presented.

RESULTS

After participants without gradable retinal photographs were excluded, 3340 people (1884 women, 1456 men) were considered at risk of CHD death. Table 1 presents the baseline characteristics of women and men in this group, comparing participants in the smallest with those in the largest AVR quartiles. For both women and men, those in the smallest AVR quartile were older, had higher systolic and diastolic blood pressures and were more likely to have severe hypertension than people in the largest AVR quartile. Over nine years 192 (78 women, 114 men) participants died of CHD.

In women aged ⩽ 75 years (n = 1565), those in the smallest AVR quartile had three times the crude rate of CHD death of those in the largest quartile (p for trend = 0.02) (table 2). No significant trends were observed in women > 75 years (n = 319) or men (n = 1456).

Table 3 presents the relationship between AVR, its components (arteriolar and venular calibres) and CHD death. When single vessel parameters were assessed in model 1, smaller retinal arteriolar and larger venular calibre were non-significantly associated with a modestly higher risk of CHD death in women aged ⩽ 75 years (RR 1.3 and 1.5 per SD change, respectively). Only AVR was associated with CHD death, with each SD lowering of AVR associated with a 1.5-fold greater risk of CHD death (RR 1.5, 95% CI 1.1 to 2.2). When both arteriolar and venular calibres were entered into model 2 simultaneously, both predicted a twofold higher risk of CHD death in women aged ⩽ 75 years (RR per SD decrease in arteriolar calibre 1.9, 95% CI 1.0 to 3.5; RR per SD increase in venular calibre 2.0, 95% CI 1.1 to 3.6). These associations were confirmed in model 3 with venule-adjusted arteriolar calibre and arteriole-adjusted venular calibre. In men aged ⩽ 75 years, larger venular calibre was associated with twice the risk of CHD death in all three multivariate models (RR per SD increase in venular calibre 1.8, 95% CI 1.1 to 2.7, model 2) (table 3). In women and men aged > 75 years, the estimated RR per SD change in these parameters remained close to unity and was not associated with CHD death in any of the models.

We further analysed the groups stratified by presence of diabetes and severe hypertension with both models 1 and 3. In women ⩽ 75 years without diabetes (n = 1476) or with severe hypertension (n = 679), the relationships between CHD death and smaller arteriolar calibre, larger venular calibre and smaller AVR remained significant and of similar magnitude (table 4). In men ⩽ 75 years the link between arteriole-adjusted venular calibre and CHD death was evident only in men without severe hypertension.

DISCUSSION

In this population-based prospective study, we found that retinal vascular calibre predicted CHD death independent of traditional cardiovascular risk factors in men and women aged 49–75 years, but not in older people. After multivariate adjustment, each SD increase in venular calibre predicted a 1.5–2-fold higher risk of CHD death in men and women. Each SD decrease in arteriolar calibre predicted a 1.3–2-fold higher risk of CHD death in women only, which supports the hypothesis that microvascular disease may be more prominent in CHD among women.[11–13 30]

We found that each SD decrease in AVR predicted a 1.5-fold higher risk of CHD death in women aged 49–75 years, supporting findings from the ARIC study (RR 1.4 per SD decrease AVR in women aged 49–73)[17] and the National Health Examination Survey (RR 2.4 in women aged 55–79 with retinal vascular abnormalities but no increased risk in men of the same age).[16] In the Beaver Dam Eye Study, however, AVR was not associated with all-cause or cardiovascular mortality at either age (43–74 years, ⩾ 75 years) or sex (men, women) subgroups.[31]

To the best of our knowledge, the current study is the first not only to examine the AVR but also specifically to examine arteriolar and venular calibres and CHD death. AVR, the ratio of the calibre of retinal arterioles to that of venules, has the advantage of controlling for camera magnification and

Table 4 CHD deaths in women and men aged ⩽75 years, by diabetes and hypertension

	CHD death*		RR of CHD death in people ⩽75 years (per SD change)					
			Model 3†				Model 1‡	
			Venule-adjusted arteriolar calibre decrease§		Arteriole-adjusted venular calibre increase§		AVR decrease§	
Status	No at risk	No of deaths	RR	95% CI	RR	95% CI	RR	95% CI
Women ⩽75 years								
No diabetes	1476	26	1.5	1.1 to 2.22	1.5	1.0 to 2.2	1.5	1.0 to 2.2
No severe hypertension	886	9	1.1	0.5 to 2.4	1.0	0.4 to 2.4	1.0	0.5 to 2.2
Severe hypertension	679	21	1.7	1.1 to 2.8	1.6	1.1 to 2.4	1.8	1.2 to 2.8
Men ⩽75 years								
No diabetes	1104	47	1.0	0.8 to 1.3	1.3	1.0 to 1.7	1.1	0.8 to 1.4
No severe hypertension	741	24	1.2	0.8 to 1.8	1.6	1.1 to 2.3	1.4	1.0 to 2.0
Severe hypertension	469	31	1.0	0.7 to 1.4	1.2	0.8 to 1.7	1.0	0.7 to 1.5

*Number at risk and number of deaths for people with retinal photographs gradable for vessel calibre.
†Model 1: relative risk (RR) adjusted for age, systolic blood pressure and smoking.
‡Model 3: RR adjusted for the covariates in model 1 and either venule-adjusted arteriolar calibre or arteriole-adjusted venular calibre.
§Per 1 SD decrease in arteriolar calibre and arteriole to venule ratio (AVR); per 1 SD increase in venular calibre.
CHD, coronary heart disease.

refractive error but may also mask information from individual arteriolar and venular calibre components.[32 33] In this study we show that the relationship between small AVR and CHD death in women reflects both narrower arterioles and wider venules. There was a borderline significant association between AVR and CHD death in men aged 49–75 years, which strengthened after stratification and became significant in men without hypertension (but not in men with hypertension). This association in men without hypertension was driven mainly by increasing venular calibre and contrasts with the situation in women, where increasing venular calibre was associated with CHD deaths in women *with* hypertension (rather than women without hypertension) and suggests that microvascular disease processes may affect men and women differently. Our findings support proposals[31 33] that individual components of the microvasculature may convey different information and show that venular calibre may be a novel factor in predicting CHD mortality. Tedeschi-Reiner and colleagues[14] reported that the severity of retinal artery atherosclerosis correlates with severity of coronary artery disease; however, mild degrees of retinal artery atherosclerosis (present mainly as arteriolar narrowing), were not related to coronary artery disease. Our results are consistent with their observations and suggest that mild retinal arteriolar atherosclerosis (arteriolar narrowing) may be associated with coronary microvascular disease rather than coronary artery (macrovascular) disease, whereas more severe signs of retinal artery atherosclerosis—for example, retinopathy, haemorrhages—are related to coronary artery disease.

Wider venular calibre has been linked to several traditional CHD risk factors, namely smoking, systemic inflammation, higher total serum cholesterol, measures of atherosclerosis and obesity.[21 33 34] Wider venules possibly are a marker for the severity of these risk factors, just as arteriolar narrowing is a marker for the severity of hypertensive damage.[35]

Strengths of our study include its population-based sample with high participation rate, well-documented retinal microvascular signs in multiple retinal photography fields, objective measures of retinal vessel calibres, and ascertainment of CHD deaths by validated NDI data. The following limitations of the study should be considered when interpreting the findings. We did not image the coronary microvasculature directly—rather, we assumed that certain retinal microvasculature changes mirror coronary microcirculatory changes. This seems to be a reasonable assumption, as the coronary and retinal small vessels change similarly with hypertension[17] and coronary microvascular disease may be part of a systemic microvascular disorder.[36 37] Although we collected information on and controlled for important confounders, other unmeasured factors (for example, use of vasodilator drugs and other subclinical vascular co-morbidities) could have affected or confounded the study findings.

About 16% of the participants who had died of CHD did not have gradable photographs for the assessment of retinal microvascular signs, which might have introduced an element of selection bias. However, of those without gradable photographs, 62% had severe hypertension and hence would be highly likely to have signs of retinal microvascular damage, and their exclusion is likely to have weakened the associations observed.

In our study, neither total serum cholesterol nor high density lipoprotein (HDL) cholesterol were considered confounders in the analysis, as they were not associated with CHD mortality. Additionally, inclusion of these variables in the models resulted in a significant loss of power, as 326 participants and 34 CHD death cases did not have total cholesterol and HDL cholesterol data (9.8% of the study population and 17.7% of total CHD cases). Nevertheless, adjustment for these variables did not change the pattern or strength of the associations (for example, in women 49–75 years, each SD increase in venular calibre was associated with RR 1.54, 95% CI 0.80 to 2.30 of CHD death).

Finally, the number of CHD deaths was small and our findings need confirmation in other populations. Future research areas include the role of retinal arterioles and venules as novel risk factors in CHD risk assessment, and the contribution of microvascular disease to CHD in men and women.

In summary, in this Australian population-based cohort, we showed that larger retinal venular calibre independently predicted a 1.5–2-fold higher risk of CHD death in both men and women aged 49–75, whereas smaller arteriolar calibre and AVR also predicted a 1.5–2-fold higher risk of CHD death, but only in women aged 49–75. Our findings, if confirmed in other populations, imply that microvascular disease processes may have a more prominent role in CHD pathogenesis in women and suggest a possible role for retinal venules and arterioles in CHD risk assessment in both men and women.

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