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Aortic coarctation and the retinal microvasculature☆,☆☆

Laurianne Le Gloan [a], Hadi Chakor [a], Lise-Andrée Mercier [a], Paul Harasymowycz [c], Annie Dore [a], Pierre Lachapelle [d], Josephine Pressacco [b], Bernard Thibault [a], François Marcotte [a], Anna Proietti [a], Hugues Leduc [e], Blandine Mondésert [a], François-Pierre Mongeon [a], Jean-Claude Tardif [a,e], Paul Khairy [a,e,*]

[a] Department of Medicine, Montreal Heart Institute, Université de Montréal, Montreal, Canada
[b] Department of Radiology, Montreal Heart Institute, Université de Montréal, Montreal, Canada
[c] Department of Ophthalmology, Hôpital Maisonneuve-Rosemont, Université de Montréal, Montreal, Canada
[d] Department of Ophthalmology, Montreal Children's Hospital Research Institute, McGill University, Montreal, Canada
[e] Montreal Health Innovations Coordinating Center (MHICC), Université de Montréal, Montreal, Canada

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ABSTRACT

Background: Aortic coarctation has been associated with generalized vascular disease, yet little is known about retinal vascular patterns and their changes over time.
Objectives: The aim of this study is to characterize the nature and extent of retinal vascular disease in adults with aortic coarctation, and explore age-related effects and associations with cardiovascular outcomes.
Methods: A prospective cross-sectional seroepidemiological study was conducted on 60 consecutive adults with repaired aortic coarctation, age 42.4 ± 14.1 years, 61.7% male. In addition to detailed questionnaires, imaging studies, and laboratory testing, high-quality retinal images were acquired by 45° nonmydriatic digital funduscopy.
Results: No patient had evidence of hypertensive retinopathy. A distinctive vascular pattern characterized by bilaterally symmetric tortuosity of retinal arteries and veins was observed. Arterial tortuosity was abnormal in 98.3% of patients and decreased with age ($P = 0.0005$). In patients ≥45 years, a 1-point increase in the arterial tortuosity score was associated with a 1.5-fold higher risk of cardiovascular complications (i.e., acute coronary syndrome, stroke, cerebral aneurysm, aortic dissection/rupture) [odds ratio 1.50, 95% CI (1.01, 2.24), $P = 0.0496$]. Abnormal venous tortuosity was present in 75.0% of patients and non-significantly correlated with higher levels of serum inflammatory markers (C-reactive protein, fibrinogen, interleukin-6, and tumor necrosis factor-alpha). A higher venous tortuosity score was likewise associated with an increased risk of cardiovascular complications [odds ratio 1.86, 95% CI (1.03, 3.35), $P = 0.0392$].
Conclusions: Adults with repaired aortic coarctation exhibit a unique retinal vascular pattern characterized by excessive arterial and venous tortuosity that regresses with age. Greater tortuosity is associated with adverse cardiovascular outcomes in patients ≥45 years.

1. Introduction

Aortic coarctation is a common congenital defect characterized by narrowing of the aortic arch, typically near the insertion site of the ductus arteriosus [1]. Despite advances in percutaneous interventions, surgical repair, and medical therapies, long-term prognosis is marred by morbidity and excess mortality related to vascular complications such as systemic arterial hypertension, accelerated coronary atherosclerosis, aortic dissection and rupture, and cerebrovascular accidents [2–4]. Although the pathogenesis remains poorly understood, intrinsic vascular abnormalities have been hypothesized to contribute to these late-onset adverse outcomes that cannot be reliably predicted by standard factors, such as severity of the initial obstruction or type of repair.

The ocular fundus is the only location in the body where blood vessels can be visualized. In other patient populations, retinal vascular changes have been associated with acute coronary syndromes, stroke, systemic biomarkers of endothelial function, and cardiovascular mortality, independent of traditional cardiovascular risk factors [5–7]. Despite concerns expressed as early as 1948 about retinal vascular abnormalities in patients with aortic coarctation [8,9], few studies

Abbreviations: A/V, Arteriovenous; CAIAR, Computer Assisted Image Analysis of the Retina; CRAE, Central retinal artery equivalent; CRVE, Central retinal vein equivalent; MRI, Magnetic resonance imaging; SIVA, Singapore "I" Vessel Assessment.

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* Corresponding author at: Montreal Heart Institute Adult Congenital Center, 5000 Bélanger E., Montreal, Quebec, Canada, H1T 1C8. Tel.: +1 514 376 3330x3652; fax: +1 514 593 2581.
E-mail address: paul.khairy@umontreal.ca (P. Khairy).

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have commented on fundoscopic findings [10] and none have explored correlations with cardiovascular events. Leveraging advances in digital fundoscopic technology, we sought to characterize retinal microvascular patterns in adults with repaired aortic coarctation, quantify the prevalence and extent of retinal vascular changes, and explore associations with age and adverse cardiovascular outcomes.

2. Material and methods

2.1. Study population

A total of 60 adults (≥18 years of age) with repaired aortic coarctation were prospectively enrolled from the Montreal Heart Institute Adult Congenital Centre between June 2010 and December 2012. Patients with Turner syndrome, contraindications to magnetic resonance imaging (MRI), or concomitant forms of congenital heart disease (other than bicuspid aortic valve and repaired simple shunt lesions) were excluded. The study protocol was approved by the Montreal Heart Institute Review Board and all participants provided written informed consent.

2.2. Study design and clinical assessment

A prospective cross-sectional seroepidemiological study was conducted consisting of a baseline questionnaire, physical examination, two-dimensional and M-mode Doppler echocardiography, laboratory testing, cerebral MRI, and bilateral digital fundoscopy.

The clinical assessment included demographic variables, height, weight, body mass index, associated defects (i.e., bicuspid aortic valve or shunt lesion), surgical and interventional history, cardiovascular risk factors [i.e., systemic arterial hypertension, hypercholesterolemia, diabetes mellitus, family history of cardiovascular disease (first degree male relative under 55 years or female relative under 65 years), and current cigarette smoking], pharmacological therapies, comorbidities, and cardiac and cerebrovascular disease (e.g., acute coronary syndromes, established coronary artery disease, stroke, transient ischemic attack, aortic dissection or rupture, and previously diagnosed cerebral aneurysms). Blood pressure was obtained by averaging three consecutive measurements at 5-min intervals separately in the right arm and right leg [11].

Echocardiographic assessment included left ventricular mass, aortic root dimensions at various levels (i.e., aortic annulus, sinuses of Valsalva, sinotubular junction, and proximal ascending aorta) and residual gradient at the site of the aortic isthmus. Due to cost constraints, cardiac MRI was performed if deemed clinically indicated, with aortic dimensions retained for analyses. Magnetic resonance angiography of the intracranial arteries was conducted using a 1.5-Tesla scanner (Philips, Netherlands) with source data reviewed in three orthogonal planes (field of view 200 mm; field of view phase 75; section thickness 0.83 mm). Post processing maximum intensity projection images were generated for multiplanar reformatting.

A single venous blood sample was drawn. After centrifugation at 3500 rpm at 4 °C for 15 min, samples were collected and stored at −80 °C until assayed. Standard methods were used to quantify serum concentrations of potassium, creatinine, lipids [i.e., total cholesterol, low- (LDL) and high-density (HDL) lipoproteins, and triglycerides], high-sensitivity C-reactive protein (CRP), and plasma fibrinogen levels. Serum levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) were determined by enzyme-linked immunosorbent assays (R&D systems, Germany).

2.3. Ophthalmic evaluation

The ophthalmology team charged with obtaining, processing, and interpreting digital retinal images was blinded to the patient's clinical history. After 5 min of dark adaptation, a 45° funduscopic examination was performed to acquire high-quality images using a Canon 9 megapixel non-mydriatic digital camera (CR-DGI 40D, Canon USA, Melville, NY) with a retinal vessel analysis software (Singapore "I" Vessel Assessment, version 1.0, 2010) [12]. The exam, which lasted approximately 15 min, was performed in a sitting position with the patient's chin on a chin rest and forehead pressed against a headrest. Patients were asked to focus on a fixation target. Detailed images of the macula and posterior pole vessels were obtained. Pictures were taken simultaneously on right and left eyes and centered on optic disks.

As illustrated in Fig. 1, all vessel segments coursing through the area between one and two times the optic disk diameter, extending from its outer boundary, were traced and identified as arteries or veins. Bilateral central retinal artery and vein diameters were measured semi-automatically by means of the SIVA program, from which the mean arterio-venous (A/V) ratio was calculated. Tortuosity of retinal arteries and veins, defined as the integral of the curvature square along the vessel path normalized by path length, was quantified by a previously described semi-automatic method using the validated Computer Assisted Image Analysis of the Retina (CAIAR) program [13–15]. CAIAR identifies vessel segments (typically 10 to 16 per eye) and determines tortuosity measurements for each segment beyond a 120-pixel diameter circle centered on the optic disc (to exclude overlapping vessels emerging from the disc) to a diameter of 400 pixels (equivalent to an area of 100 mm^2). Average measurements were summarized as a tortuosity score separately for arteries and veins. Units of tortuosity represent a ratio and are, therefore, continuous and dimensionless [14].

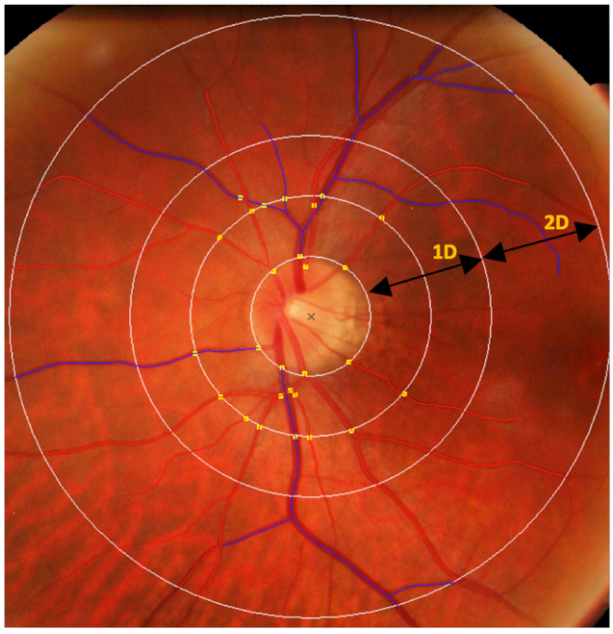

Fig. 1. Retinal vessel calibre and tortuosity scores. Shown is a 45° fundus retinal image centered on the optic disk. For illustrative purposes, retinal arteries are indicated in red and veins in blue. Retinal vessel calibres and tortuosity scores were measured semi-automatically for all vessel segments coursing through the area between one (1D) and two (2D) times the diameter of the optic disk. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.4. Statistical analysis

Continuous variables are summarized by mean ± standard deviation or median and interquartile range (IQR; 25th, 75th percentile), depending on their distribution. Categorical variables are represented by frequencies and percentages. Baseline variables according to severity of retinal arterial tortuosity, classified as normal (≤5) or mild (>5 and ≤7), moderate (>7 and ≤9), and severe (>9), were compared by nonparametric Kruskal Wallis, chi-square, or Fisher Exact tests, where appropriate (Table 1). Prevalence values and their 95% confidence intervals (CI) were estimated for abnormal arterial and venous tortuosity scores and A/V ratio. Factors associated with arterial (Table 2) and venous (Table 3) tortuosity scores and the A/V ratio (Table 4) were explored in univariate and multivariate linear regression models. Variables associated with *P*-values <0.2 in univariate analyses were entered into automated stepwise multivariate regression models. Factors associated with adverse cardiovascular outcomes (i.e., acute coronary syndrome, stroke, transient ischemic attack, cerebral aneurysm, aortic dissection or rupture) were explored in logistic regression analyses that included first-order interaction terms between age and tortuosity scores. Two-tailed *P*-values <0.05 were considered statistically significant. Statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC).

3. Results

3.1. Baseline characteristics

A total of 60 patients, age 42.4 ± 14.1 years, 61.7% male were prospectively enrolled. Baseline characteristics are summarized in Table 1. The aortic valve was bicuspid in 27 (45.0%) patients. Aortic coarctation repair was performed at a median age of 8.4 (IQR 4.3, 20.8) years. Fourteen (23.3%) patients had primary balloon dilation and/or stenting, whereas 46 (76.7%) had surgical repair consisting of a termino-terminal anastomosis in 30 (50.0%), subclavian flap in 9 (15.0%), and patch aortoplasty or bypass graft in 7 (11.7%). Cardiovascular risk factors included hypercholesterolemia in 13 (21.7%) patients, hypertension in 28 (46.7%), diabetes in 1 (1.7%), family history of premature coronary artery disease in 10 (16.7%), and active cigarette smoking in 9 (15.0%).

3.2. Retinal vessel dimensions and the A/V ratio

Nonmydriatic fundoscopic high-quality digital retinal images were successfully acquired in all patients. No patient had evidence of a retinal

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Table 1
Patient characteristics according to severity of retinal arterial tortuosity.

	All patients $N = 60$	Normal or mild tortuosity $N = 21$	Moderate tortuosity $N = 18$	Severe tortuosity $N = 21$	*P*-value
Age, years	42.4 ± 14.1	48.3 ± 14.2	45.1 ± 13.6	34.4 ± 10.7	0.0025
Male sex, *N* (%)	37 (61.7)	11 (52.4)	9 (50.0)	17 (81.0)	0.0778
Height, cm	169.2 ± 9.9	168.0 ± 10.1	166.2 ± 10.4	173.1 ± 8.3	0.0716
Weight, kg	74.6 ± 17.4	70.5 ± 16.9	73.0 ± 14.2	80.0 ± 19.7	0.1868
Body mass index, kg/m^2	25.9 ± 4.8	24.8 ± 4.2	26.3 ± 4.0	26.5 ± 6.0	0.4425
Coarctation repair, N (%)					
Termino-terminal anastomosis	30 (50.0)	9 (42.9)	11 (61.1)	10 (47.6)	0.5053
Sub-clavian flap	9 (15.0)	4 (19.0)	2 (11.1)	3 (14.3)	0.9023
Patch aortoplasty or bypass graft	7 (11.7)	3 (14.3)	3 (16.7)	1 (4.8)	0.5441
Balloon dilation and/or stent	14 (23.3)	5 (23.8)	2 (11.1)	7 (33.3)	0.2537
Cardiovascular risk factors, N (%)					
Hypercholesterolemia	13 (21.7)	5 (23.8)	4 (22.2)	4 (19.0)	0.9279
Hypertension	28 (46.7)	8 (38.1)	10 (55.6)	10 (47.6)	0.5491
Diabetes	1 (1.7)	1 (4.8)	0 (0)	0 (0)	0.6500
Family history	10 (16.7)	3 (14.3)	2 (11.1)	5 (23.8)	0.6832
Current cigarette smoking	9 (15.0)	2 (9.5)	3 (16.7)	4 (19.0)	0.7376
Blood pressure, mm Hg					
Right arm: systolic blood pressure	132 ± 21	130 ± 21	135 ± 20	130 ± 22	0.7668
Right arm: diastolic blood pressure	72 ± 10	73 ± 9	71 ± 12	71 ± 9	0.8273
Right leg: systolic blood pressure	150 ± 30	157 ± 30	148 ± 29	145 ± 30	0.3641
Right leg: diastolic blood pressure	72 ± 13	72 ± 11	75 ± 14	69 ± 15	0.3378
Laboratory tests					
Potassium, mmol/L	3.9 ± 0.2	4.0 ± 0.2	3.8 ± 0.3	3.8 ± 0.2	0.0886
Creatinine, μmol/L	77.3 ± 14.3	80.4 ± 15.0	73.0 ± 14.2	78.0 ± 13.6	0.2719
Glucose, mmol/L	5.4 ± 0.7	5.6 ± 0.8	5.1 ± 0.6	5.4 ± 0.7	0.1320
Total cholesterol, mmol/L	4.5 ± 1.1	4.6 ± 1.1	4.8 ± 1.3	4.2 ± 0.7	0.1465
LDL cholesterol, mmol/L	2.7 ± 0.9	2.7 ± 0.9	2.9 ± 1.1	2.5 ± 0.7	0.5134
HDL cholesterol, mmol/L	1.6 ± 0.9	1.4 ± 0.4	1.6 ± 0.7	1.7 ± 1.3	0.6444
Triglycerides, mmol/L	1.2 ± 0.6	1.1 ± 0.6	1.3 ± 0.7	1.1 ± 0.5	0.4935
C-reactive protein[a], mg/L	1.2 (0.5, 3.9)	0.9 (0.4, 2.3)	1.2 (0.6, 3.6)	1.9 (0.5, 5.0)	0.1540
Fibrinogen, g/L	3.2 ± 0.6	3.1 ± 0.6	3.3 ± 0.6	3.1 ± 0.7	0.6147
Interleukin-6[a], pg/mL	1.1 (0.9, 1.8)	1.1 (0.8, 1.5)	1.1 (0.9, 1.9)	1.6 (0.8, 2.1)	0.3374
Tumor necrosis factor-alpha, pg/mL	1.9 ± 0.5	2.0 ± 0.4	1.8 ± 0.4	1.9 ± 0.6	0.2919
Medical therapy, N (%)					
Diuretics	7 (11.7)	1 (4.8)	5 (27.8)	1 (4.8)	0.1943
Beta-blockers	12 (20.0)	3 (14.3)	5 (27.8)	4 (19.0)	0.6613
Aspirin	10 (16.7)	3 (14.3)	4 (22.2)	3 (14.3)	0.7550
ACE-inhibitor or ARB	21 (35.0)	5 (23.8)	8 (44.4)	8 (38.1)	0.3772
Statin	13 (21.7)	5 (23.8)	4 (22.2)	4 (19.0)	0.9279
Echocardiographic parameters					
Bicuspid aortic valve, N (%)	27 (45.0)	13 (61.9)	8 (44.4)	6 (28.6)	0.0946
Left ventricular mass, g	93.1 ± 29.4	102.9 ± 34.2	97.8 ± 30.8	79.4 ± 16.7	0.0286
Aortic dimensions, mm					
Aortic annulus	22.2 ± 2.8	21.5 ± 2.7	22.5 ± 2.2	22.6 ± 3.5	0.4360
Sinus of Valsalva	32.6 ± 5.4	34.2 ± 5.4	31.8 ± 3.7	31.9 ± 6.6	0.3261
Sinotubular junction	27.3 ± 4.7	28.9 ± 4.9	26.9 ± 4.4	26.0 ± 4.6	0.2108
Proximal ascending aorta	31.4 ± 6.5	34.0 ± 7.5	31.2 ± 6.1	28.9 ± 5.1	0.0526
Residual gradient, mm Hg	14.1 ± 9.0	13.2 ± 8.1	15.4 ± 12.0	13.8 ± 6.4	0.7469

LDL denotes low-density lipoprotein; HDL, high-density lipoprotein; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.
[a] Non-normally distributed continuous variables are expressed as median and interquartile range.

Table 2
Factors associated with retinal arterial tortuosity.

	Beta-coefficient	95% confidence interval	*P*-value
Univariate analysis*			
Age, year	−0.370	−0.092, −0.019	0.0036
Male sex	0.240	−0.066, 2.104	0.0652
Height, cm	0.197	−0.013, 0.096	0.1313
Weight, kg	0.169	−0.011, 0.051	0.1966
Potassium, mmol/L	−0.284	−4.601, −0.277	0.0277
Total cholesterol, mmol/L	−0.205	−0.918, 0.104	0.1164
Bicuspid aortic valve	−0.251	−2.101, 0.014	0.0530
Left ventricular mass, g	−0.350	−0.042, −0.007	0.0077
Sinotubular junction dimension, mm	−0.219	−0.208, 0.029	0.1343
Proximal ascending aorta dimension, mm	−0.255	−0.162, 0.003	0.0580
Multivariate analysis			
Age, year	−0.447	−0.102, −0.031	0.0005
Bicuspid aortic valve	−2.714	−2.292, −0.344	0.0089

* Shown are the variables associated with *P*-values <0.2 in univariate analyses, which were therefore further considered in the automated stepwise multivariate model

hemorrhage, microaneurysm, hard exudate, cotton-wool spot, optic disk swelling, or macular edema.

The mean central retinal artery (CRAE) dimensions were 155.2 ± 18.0 μm and 156.5 ± 18.2 μm in right and left eyes, respectively ($P = 0.531$). Mean central retinal vein equivalent (CRVE) dimensions in right and left eyes were 242.3 ± 34.1 μm and 240.3 ± 33.7 μm ($P = 0.6422$). The A/V ratio averaged 0.65 ± 0.07 and was abnormal (i.e., <0.7) in 48 [80.0%, 95% CI (69.9%, 90.1%)] patients. The A/V ratio did not correlate with age ($P = 0.7585$) and was non-significantly lower in patients with a family history of premature coronary artery disease [beta-coefficient −0.033, 95% CI (−0.082, 0.017), $P = 0.1923$] and with higher serum creatinine levels [beta-coefficient −0.011 per 10 mmol/L, 95% CI (−0.024, 0.002), $P = 0.0975$]. No statistically significant univariate or multivariate predictors of the A/V ratio were identified.

3.3. Retinal arterial tortuosity

A distinctive vascular pattern was observed that was characterized by bilaterally symmetric tortuosity of retinal arteries and veins, as

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Table 3
Factors associated with retinal venous tortuosity.

	Beta-coefficient	95% confidence interval	*P*-value
Univariate analysis*			
Age, year	−0.241	−0.051, 0.001	0.0632
Statin	−0.302	−1.935, −0.182	0.0188
Creatinine, mmol/L	0.193	−0.007, 0.046	0.1397
C−reactive protein, mg/L	0.231	−0.007, 0.113	0.0810
Fibrinogen, g/L	0.192	−0.143, 1.054	0.1427
Interleukin-6, pg/mL	0.177	−0.095, 0.510	0.0530
Tumor necrosis factor-alpha, pg/mL	0.195	−0.191, 1.377	0.1353
Left ventricular mass, g	−0.219	−0.082, −0.028	0.0280
Sinotubular junction dimension, mm	−0.377	−0.189, −0.030	0.0083
Proximal ascending aorta dimension, mm	−0.203	−0.095, 0.013	0.1343
Multivariate analysis			
Sinotubular junction dimension, mm	−0.101	−0.188, −0.014	0.0242

* Shown are the variables associated with *P*-values <0.2 in univariate analyses, which were therefore further considered in the automated stepwise multivariate model.

illustrated in Fig. 2. Mean arterial tortuosity scores were 8.4 ± 2.5 and 8.0 ± 2.4 in right and left eyes, respectively ($P = 0.3202$). Abnormal arterial tortuosity was present in 59 [98.3%, 95% CI (95.1%, 100%)] patients and was classified as mild (i.e., >5 and ≤7) in 20 (33.3%), moderate (i.e., >7 and ≤9) in 18 (30.0%), and severe (i.e., >9) in 21 (35.0%). Factors associated with arterial tortuosity score in univariate and multivariate linear regression analyses are summarized in Table 2. The only variables independently associated with a greater degree of arterial tortuosity were younger age [beta-coefficient −0.447 per year, 95% CI (−0.102, −0.031), $P = 0.0005$] and presence of a bicuspid aortic valve [beta-coefficient −2.714, 95% CI (−2.292, −0.344), $P = 0.0089$]. The association between decreasing retinal arterial tortuosity and older age is graphically depicted in Fig. 3.

3.4. Retinal venous tortuosity

Average venous tortuosity scores were 6.0 ± 1.8 and 6.0 ± 1.7 in right and left eyes, respectively ($P = 0.7749$). Abnormal venous tortuosity was present in 45 [75.0%, 95% CI (64.0%, 86.0%)] patients and was mild in 32 (53.3%), moderate in 11 (18.3%), and severe in 2 (3.3%). Factors associated with venous tortuosity in univariate and multivariate linear regression analyses are summarized in Table 3. A non-significant correlation was observed between higher levels of serum inflammatory markers (i.e., C-reactive protein, fibrinogen, interleukin-6, and tumor necrosis factor-alpha) and retinal venous tortuosity. In multivariate analyses, the only factor independently associated with venous tortuosity was the aortic root size measured at the level of the sinotubular junction [beta-coefficient −0.101 per mm, 95% CI (−0.188, −0.014), $P = 0.0242$].

Table 4
Factors associated with the retinal arterio-venous (A/V) ratio.

	Beta-coefficient	95% confidence interval	*P*-value
Univariate analysis*			
Height, cm	−0.001	−0.003, 0.001	0.1790
Age at surgery, year	0.001	0.000, 0.002	0.1873
Family history of premature CAD	−0.033	−0.082, 0.017	0.1923
Creatinine, mmol/L	−0.001	−0.002, 0.000	0.0975

* Shown are the variables associated with *P*-values <0.2 in univariate analyses, which were therefore further considered in the automated stepwise multivariate model.

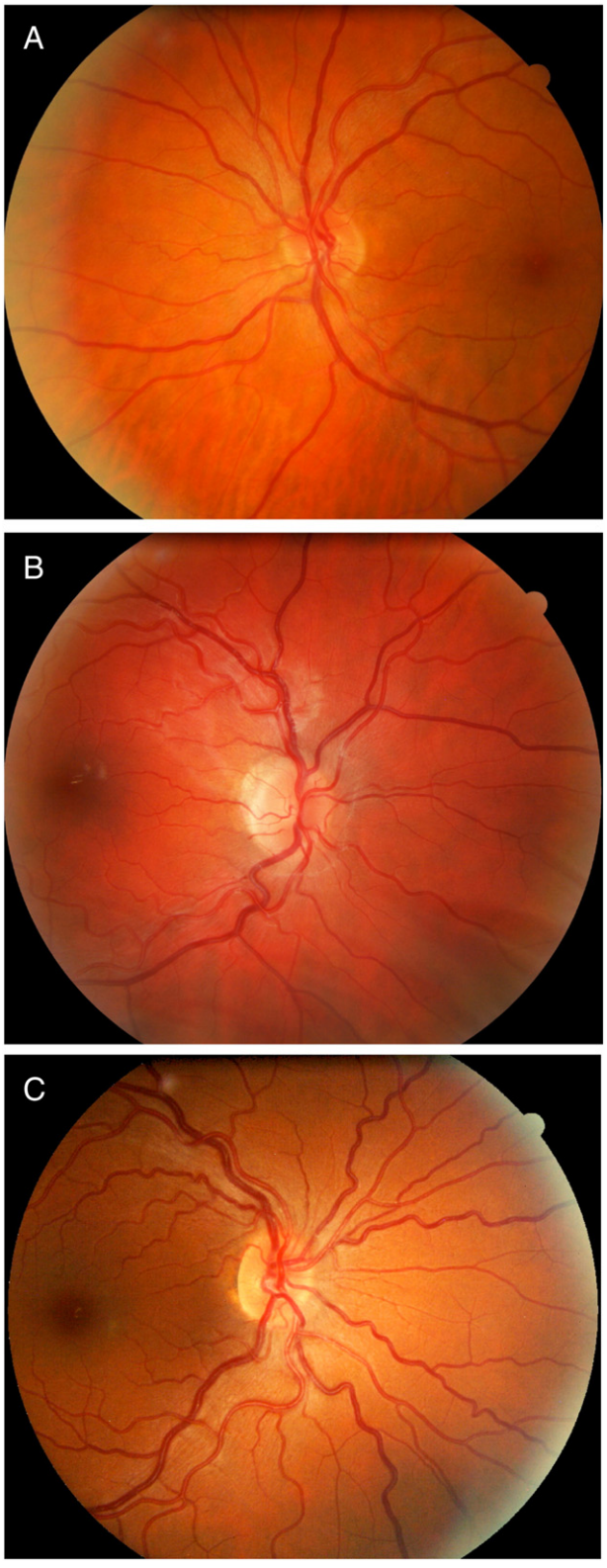

Fig. 2. Retinal vascular tortuosity. Shown are representative fundoscopic digital images in adults with repaired aortic coarctation demonstrating A) mild, B) moderate, and C) severe degrees of retinal microvascular tortuosity.

3.5. Retinal vascular tortuosity and cardiovascular outcomes

Routine screening by MRI revealed the presence of cerebral aneurysms in 2 patients, corresponding to a prevalence of 3.3%, 95% CI (0.3%, 12.0%). One patient had a 6 mm basilar aneurysm that was

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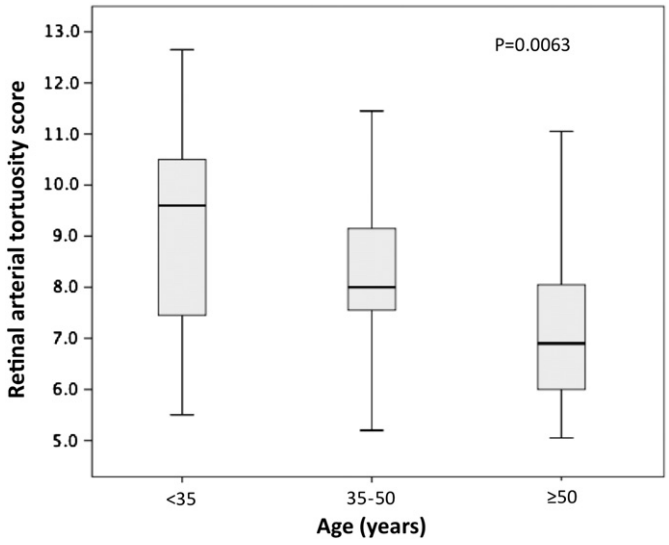

Fig. 3. Retinal arterial tortuosity score according to age. Boxplots of retinal arterial tortuosity scores are shown in patients <35, 35 to 50, and ≥50 years of age. Lower and upper edges of the box indicate lower and upper quartiles. The line in the box represents the median value. Lower and upper bars denote 10th and 90th percentiles. Note the decreasing tortuosity scores with increasing age.

subsequently coil-occluded. A second patient had two small (<5 mm) aneurysms of the right middle cerebral artery that were managed conservatively. In addition, 2 patients had acute coronary syndromes, one of whom was treated medically and the second by percutaneous coronary angioplasty. No patient suffered a stroke, transient ischemic attack, aortic dissection, or aortic rupture, nor had coronary artery bypass or peripheral vascular surgery.

In exploring associations between retinal vascular tortuosity and cardiovascular outcomes, a significant interaction was identified between age and arterial and venous tortuosity. In patients under 45 years of age, arterial and venous tortuosity scores were not predictive of cardiovascular outcomes. By contrast, in patients 45 years or older, a 1-point increase in arterial tortuosity was associated with 1.5-fold higher risk of an adverse cardiovascular outcome [odds ratio 1.50, 95% CI (1.01, 2.24), $P = 0.0496$]. Similarly, a 1-point higher venous tortuosity score was associated with a 1.9-fold increased risk [odds ratio 1.86, 95% CI (1.03, 3.35), $P = 0.0392$] in patients ≥45 years.

4. Discussion

Despite uncertainties as to whether hemodynamic sequelae or independent pathophysiological processes are implicated, evidence suggests that aortic coarctation is associated with a more generalized vasculopathy. Fundoscopy, which offers a non-invasive means to visualizing microvasculature, carries the potential to provide valuable diagnostic and prognostic information in patients with aortic coarctation. Herein, we report the largest and most extensive systematic appraisal of retinal microvascular findings in adults with repaired aortic coarctation. Retinal microvascularization was assessed by state-of-the-art digital fundoscopy with semi-automated quantification of vessel diameters and tortuosity. Key findings include: 1) A distinctive microvascular pattern characterized by bilaterally symmetric tortuosity of retinal arteries and veins that regresses with age; 2) Absence of hypertensive retinopathy; 3) A reduction in the A/V ratio; and 4) An association between higher retinal arterial and venous tortuosity scores in patients 45 years or older and adverse cardiovascular outcomes.

Our findings support Granstrom's early qualitative descriptions of pronounced tortuosity of the retinal arteries and absence of hypertensive changes in patients with predominantly unoperated aortic coarctation [8]. While we quantified a reduction in tortuosity with increasing age in adults with repaired aortic coarctation, retinal hypertensive changes (e.g., arteriovenous nicking, lipid exudates, intraretinal edema, and cotton wool spots) [9] were strikingly absent despite known hypertension in 47% of patients. Nevertheless, the high prevalence of hypertension likely contributed to the abnormally low A/V ratios identified in 80% of patients. Previously described determinants of smaller retinal artery calibre in populations without aortic coarctation include higher systolic and diastolic blood pressure and hypertension, whereas smoking, obesity, diabetes, dyslipidemia, and serum markers of inflammation have been associated with larger retinal veins [5]. The non-significant correlation observed between coronary artery disease and lower A/V ratio in the current study is, therefore, consistent with prior reports [6]. The trend towards lower A/V ratios with higher serum creatinine levels is likewise congruent with studies linking severity of retinopathy with kidney function in cohorts of adults with chronic renal insufficiency [16].

Our study provides empirical evidence that retinal arterial "corkscrew-shaped" [8,17,18] tortuosity and, to a lesser extent, venous tortuosity [10] are hallmark attributes in adults with repaired aortic coarctation. Over 98% of patients had abnormal retinal arterial tortuosity, whereas 75% had increased venous tortuosity. Fluorescence angiographic studies performed in 1970 in 25 adults with aortic coarctation found that nearly half the patients had tortuous vessels prior to surgery, with a pattern that persisted up to 4 months post-operatively [19]. A more recent series of 10 patients reported that vascular tortuosity persisted a minimum of 3 years following initial repair [10]. Investigators have hypothesized that arterial hypertension above the isthmic constriction site may act as a vasculogenic stimulus leading to proliferation of a capillary meshwork in the choroidea and retina beginning in fetal life [19], and that increased retinal arterial pulse pressure and pliable vessel walls may contribute to the pathogenic pattern [20]. Considering that aortic coarctation can impede the delivery of oxygen-rich blood, hypoxia may also serve as stimulus for vascular remodelling. In premature children, hypoxia results in retinal arterial tortuosity and venous dilation [21]. Obstructive sleep apnea [22] and high altitude [23] have also been associated with increased retinal arterial and venous tortuosity.

Our observation that vascular tortuosity decreases over time in adults with repaired aortic coarctation suggests that vascular changes are acquired and, at least in part, reversible. These finding are supported by a pre-clinical model of experimentally induced aortic coarctation in 96 dogs [24]. Venular dilation and arterial tortuosity progressively appeared after partially occluding the aorta and were dependent on the degree and duration of aortic narrowing [24]. Importantly, we report that higher arterial and venous tortuosity scores are associated with adverse cardiovascular outcomes in older adults (i.e., ≥45 years) with repaired aortic coarctation. While underlying reasons remain to be elucidated, it can be hypothesized that a blunted positive vascular remodelling response following aortic coarctation repair may convey a higher risk of vascular complications. Considering that proinflammatory cytokines are associated with vascular remodelling [25], inflammation may be one of several potential factors implicated in the pathophysiological process. Indeed, a trend was observed between venous tortuosity and higher levels of serum inflammatory markers (i.e., C-reactive protein, fibrinogen, interleukin-6, and tumor necrosis factor-alpha), a finding consistent with previous studies [5,7]. From a clinical perspective, these observations introduce the possibility that serial fundoscopic monitoring may be of prognostic value in identifying patients at higher risk of cardiovascular complications.

4.1. Limitations

The study is cross-sectional in nature such that cause-and-effect relationships cannot be inferred. While the study was deliberately designed to quantify prevalence rates of retinal vascular anomalies and assess multiple associations, it should be considered exploratory

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in nature and, hence, hypothesis-generating. Although the study includes the largest population of adults with aortic coarctation to undergo fundoscopic studies to date, regression analyses were limited by the sample size. In particular, the few cardiovascular events precluded multivariate logistic regression analyses. Moreover, serial assessment was not performed to quantify intra-patient changes in retinal micovascular metrics over time such that average rates of change cannot be estimated.

Conclusions

Adults with repaired aortic coarctation exhibit a pathognomonic retinal vascular pattern characterized by marked arterial and venous tortuosity accompanied by a reduced A/V ratio. The degree of arterial and venous tortuosity decreases with age, suggesting the presence of a reversible component and potential for positive vascular remodelling. In exploratory analyses, a higher degree of arterial and venous tortuosity is associated with adverse cardiovascular outcomes in adults 45 years or older. These provocative observations, which merit confirmation by large prospective studies, raise the possibility that a blunted positive vascular remodelling response portends a poorer prognosis such that serial fundoscopic testing may potentially identify patients at higher risk of cardiovascular complications.

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