Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Multimodal Retinal Imaging Identifies a Persistent Microvascular Phenotype in Repaired Aortic Coarctation: An Oculomics Study

Rita ANJOS

rita.s.anjos@gmail.com

ULS Sao Jose https://orcid.org/0000-0002-9058-5836

Rui Anjos

João Rato

Susana Cordeiro

Nuno Rodrigues Alves

Unidade Local de Saúde de São José https://orcid.org/0009-0001-3329-1014

Cristina Ferreira

Bruno Quendera

Paulo Gouveia

Liliana Caldeira

Pedro Serrasqueiro

Tânia Melo

Luis Abegão Pinto

https://orcid.org/0000-0002-9960-7579

Angela Carneiro

University of Porto

Article

Keywords: Oculomics, Optical coherence tomography angiography, Retinal vessel density, Choroidal vascularity index, Aortic coarctation, Microvascular remodelling

Posted Date: July 15th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10019641/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: There is no conflict of interest

Abstract

Background/Objectives:

Multimodal retinal imaging provides non-invasive access to the systemic microvasculature and has emerged as a promising oculomics tool for cardiovascular risk assessment. Repaired aortic coarctation (AoCo) represents a model of early-life pressure overload and lifelong vascular remodelling, yet no study has characterised the retinal and choroidal microvascular phenotype in this population. We aimed to determine whether quantitative retinal and choroidal imaging biomarkers reflect the degree of systemic microvascular dysfunction in repaired AoCo.

Subjects/Methods:

In this cross-sectional case–control study, 98 subjects (49 repaired AoCo and 49 age- and sex-matched controls) underwent multimodal ocular imaging. Macular vessel density (VD) by optical coherence tomography angiography (OCTA) was the primary outcome. Secondary measures included retinal vascular tortuosity and choroidal vascularity index (CVI) by enhanced depth imaging OCT.

Results

AoCo patients exhibited significantly reduced macular VD compared to controls (38.3% vs 39.5%; $p = 0.003$) and increased retinal vascular tortuosity ($p = 0.004$), independent of age, sex, axial length, and current blood pressure. CVI was also reduced ($p = 0.026$). Vessel density and tortuosity showed a graded association with markers of hypertensive burden — including systemic hypertension, residual aortic gradient, left ventricular hypertrophy, non-dipping circadian pattern, and hypertensive exercise response (all $p < 0.01$) — and were abnormal even in patients without overt clinical complications.

Conclusions

Multimodal retinal imaging identifies a persistent microvascular phenotype in repaired AoCo that tracks with cardiovascular burden. By bringing oculomics to bear on a congenital heart condition, these findings support quantitative retinal and choroidal metrics as a practical, non-invasive adjunct for identifying patients at greater long-term vascular risk.

Key messages

What was known before

Aortic coarctation (AoCo) leads to lifelong vascular complications despite anatomic repair. The retinal and choroidal microvasculature can be quantified non-invasively by OCTA and OCT, providing oculomics biomarkers of systemic vascular health across cardiovascular diseases.

What this study adds

This is the first multimodal oculomics study in repaired AoCo. Quantitative retinal and choroidal

biomarkers — vessel density, vascular tortuosity, and choroidal vascularity index — identify a persistent microvascular phenotype that tracks with cardiovascular burden, independent of current blood pressure.

How this study might affect research, practice or policy

Retinal and choroidal imaging brings the tools of oculomics to a congenital heart condition. These metrics could complement cardiovascular follow-up in AoCo, offering a non-invasive way to flag patients at greater long-term vascular risk.

STROBE compliance

This study complies with the STROBE guidelines for reporting observational studies. The completed STROBE checklist is provided as Supplementary File 1.

Introduction

Repaired aortic coarctation (AoCo) is a congenital **narrowing** of the aortic arch that imposes pressure overload from early life and **confers lifelong cardiovascular risk** despite anatomic repair, including hypertension, aortic aneurysm, coronary disease, and cerebrovascular events [1]. This ongoing burden suggests that, more than a localised defect, AoCo may have systemic vascular consequences, affecting both macro and microcirculatory networks. Whether these changes reflect a primary arteriopathy or the long-term effect of altered haemodynamics remains to be clarified[2].

The retinal vasculature provides a non-invasive window into systemic microvascular health and has emerged as a sensitive marker of early vascular dysfunction, with consistent evidence of retinal rarefaction and reduced vessel density (VD) across cardiovascular diseases [3] [4]. These findings support the use of **quantitative retinal imaging as a surrogate of systemic vascular integrity and cardiovascular risk. Optical coherence tomography (OCT)** offers **high-resolution, dye-free retinal imaging,** and its angiographic extension **(OCTA)** enables **quantitative assessment of retinal and choroidal microvasculature** through motion-contrast detection of erythrocyte flow [5].

We hypothesised that patients with repaired AoCo exhibit a persistent retinal microvascular phenotype detectable by quantitative oculomics, and that this phenotype relates to contemporaneous cardiovascular burden. We therefore conducted a cross-sectional, case–control study comparing multimodal retinal and choroidal biomarkers between patients with repaired AoCo and matched healthy controls, and explored associations with hypertension, residual gradient, left-ventricular hypertrophy, ambulatory blood-pressure patterns, and exercise responses.

Materials & Methods

Study Design and Ethics

This cross-sectional, observational, case-control study was conducted at Hospital CUF Descobertas, Hospital de Santa Cruz (Unidade Local de Saúde de Lisboa Ocidental), and NOVA Medical School, Lisbon. The study adhered to the Declaration of Helsinki and was approved by the institution of ethics Committee. Written informed consent was obtained from all participants or their legal representatives before examinations.

Participants

Patients with treated AoCo were consecutively screened from a Pediatric and Congenital Cardiology outpatient clinic. Healthy controls with normal blood pressure (BP), matched for age and sex, were recruited among non-sibling volunteers, including staff members and/or their relatives. Exclusion criteria included: (i) age <10 years; (ii) high refractive error (spherical equivalent >6.00 dioptres or astigmatism >3.00 dioptres); (iii) intraocular pressure (IOP) >24 mmHg; (iv) history of ocular trauma, surgery, or known ocular pathology; (v) systemic disease unrelated to AoCo with microvascular impact (e.g., diabetes, systemic vasculitis); and (vi) abnormal fundus findings. Eligibility was confirmed through medical record review before inclusion

Clinical and cardiovascular assessment

The following parameters were collected and analysed from exams performed within 6 months of the study visit: body mass index (BMI), history and degree of hypertension, right arm office systolic BP at rest, corrected Doppler estimated isthmic gradient at rest (considering the pre isthmic velocity) [6], presence of significant residual isthmic gradient (> 20 mmHg), presence of Doppler isthmic diastolic extension at rest, right arm systolic BP and peak Doppler estimated isthmic gradient during exercise, presence of bicuspid aortic valve, left ventricular mass index (LVMI), presence of left ventricular hypertrophy (LVH), 24-hour ambulatory BP monitoring (ABPM) systolic and diastolic values, systolic load over 24 h, daytime and nighttime systolic load. Additional data included type and number of treatment procedure(s) for coarctation, age at first procedure and antihypertensive therapy.

Definitions

Hypertension was defined per international guidelines [7,8]. An elevated BP load was indicated by a load >25% on 24-hour ABPM [9]. Patients were classified as dippers or non-dippers according to their nocturnal systolic BP fall on 24-hour ABPM: a reduction of ≥10% defined dipper status, and a reduction of <10% defined non-dipper status[10]. LVH was defined as LVMI > 115 g/m² in males and > 95 g/m² in females[11]. Systolic hypertensive exercise response was described as a systolic BP above 210/190mmHg for male/female adults, respectively, and above the 95th percentile of normative BP response to exercise in children and adolescents [12,13].

Ophthalmic Examination

At study visit, all participants underwent a standardised ophthalmic evaluation, including non-cycloplegic autorefractometry, axial length and biometry measurements (APS Haag-Streit®), IOP assessment (iCare®), and a fundus examination by a retina specialist. Arterial pressure was measured at the time of ophthalmic evaluation in the right arm using an automated sphygmomanometer after a five-minute seated rest.

Ophthalmic Imaging Protocol

All imaging was performed using the spectral-domain OCT system (Heidelberg Engineering, Germany) by two masked, experienced examiners. High-resolution macular OCT scans with Enhanced Depth Imaging (EDI) were used to assess choroidal thickness and the choroidal vascularity index (CVI). OCTA macular scans were used to quantify superficial retinal VD. **Infrared fundus images** were analysed for **retinal vascular tortuosity** using an AI-based segmentation pipeline. Two masked investigators independently reviewed all scans to ensure quality. Both assessed the entire dataset, and any discrepancies were resolved by consensus. Low-quality or artifacted images (signal strength <7) were excluded. Detailed ophthalmic imaging protocols are provided in the Supplementary Methods.

Image Analysis

Only right-eye images were included for analysis. OCTA images were analysed using OCTAVA[14], a validated, open-source analytical platform for automated vascular quantification. The **primary outcome** was **superficial vascular plexus (SVP) VD**, representing the proportion of perfused retinal tissue. Secondary metrics included vessel length density (VLD), total vessel length (TVL), mean vessel diameter, and fractal dimension (FD, branching complexity). The foveal avascular zone (FAZ) was characterised by area, perimeter, and acircularity index. The CVI was calculated from EDI-OCT as the ratio of vascular to total choroidal area [15]. Retinal vascular tortuosity was assessed using two complementary methods: (i) OCTA-derived quantitative indices with twig-size filtering[16]); (ii) **AI-derived classification from infrared images** [17]. This deep-learning classifier was developed and internally validated using five-fold cross-validation in a prior methodological study [17]; it has not yet been externally validated in independent cohorts. Detailed image processing steps are provided in the Supplementary Methods.

Outcomes and Sample Size

The primary outcome of the study was macular SCP VD. Secondary outcomes included foveal SCP FAZ area, VLD, TVL, vessel diameter, FD, and vascular tortuosity (twig 8 and twig 30) in OCTA and infrared, as well CVI in OCT-EDI images.

The sample size for the primary outcome (SCP VD) was determined to identify a mean difference in SCP VD between groups. Based on prior research reporting a mean VD of 43.44% in healthy controls and

41.27% in hypertensive patients, with a standard deviation of 3.2%, a minimum of 37 participants per group was necessary to attain 80% power at a two-sided alpha level of 0.05. These estimates are corroborated by recent meta-analytic data derived from OCTA in cases of systemic hypertension [18], as well as by device-specific reproducibility studies demonstrating standard deviations ranging from 2.5% to 4.0% for SCP measurements across various commercial platforms[19].

Statistical Analysis

Continuous variables were expressed as means and standard deviation (SD) or medians and interquartile range (IQR), as appropriate. Categorical variables were summarised as absolute and relative frequencies. Between-group comparisons of continuous variables were performed using independent t-tests or Mann–Whitney U tests, depending on distribution. Associations between retinal microvascular parameters and clinical variables were examined using linear regression models.

Normality was assessed using the Shapiro–Wilk test within each group. For non-normal data or unequal variances, robust or non-parametric tests were applied, including Kruskal–Wallis test for group comparisons, Cuzick's non-parametric test for ordered trends, and the Brown–Forsythe test for variance equality. Ordinal outcomes (retinal tortuosity grades 0/1/2) were analysed with **ordered logistic regression using robust standard errors**. The **overall association** between groups and tortuosity was evaluated with the **Wald χ^2** statistic, and p**airwise comparisons versus controls were based on the ordered logistic regression coefficients.** P -values were adjusted for multiple comparisons using the Holm method. Subgroup analyses across cardiovascular burden markers were exploratory and intended to be hypothesis-generating, given the limited number of participants in some strata. An exploratory subgroup analysis based on timing of surgical repair (≤28 days vs >28 days) is detailed in the Supplementary Methods.

All tests were two-tailed, with $p < 0.05$ considered significant. Analyses were conducted using Stata/IC 15.1 for Mac (StataCorp, College Station, TX, USA). Model diagnostics, including residual distributions, multicollinearity, and specification tests, are provided in the Supplementary Methods.

Results

Participant Characteristics

A total of ninety-eight participants were included: 49 patients with treated AoCo and 49 healthy controls. There were no significant differences observed in age, sex, axial length, and intraocular pressure (see Table 1). As anticipated, patients with AoCo exhibited elevated office systolic BP.

The quality of OCTA images was evaluated by two masked graders (Examiner 1 and Examiner 2), who were blinded to the clinical classifications of the participants. Within the AoCo group, OCTA data could not be obtained for three patients due to lack of cooperation, and seven scans were excluded owing to poor signal strength, motion artefacts, or segmentation errors, in accordance with predetermined quality

criteria. Consequently, data from 39 out of 49 patients were included in the OCTA analysis. Among the control group, five scans were similarly excluded for the same reasons. To ensure comparability, a random selection of 39 healthy controls was made from the eligible pool, resulting in a comparable age and sex distribution to the final AoCo group. A flow diagram summarising patient inclusion and exclusion is included in the Supplementary Results (Figure S1). Baseline characteristics of participants involved in the OCTA analysis are also reported in the Supplementary Results (Section 2, Table S1). The groups were comparable across all parameters, except for a higher systolic BP observed in the AoCo group (128.33 ± 16.88 mmHg versus 118.54 ± 12.17 mmHg in controls, p = 0.004).

Coarctation cohort

The age at first intervention was 4.4 ± 1.0 years, with a median of 1.15 [0.03–6.6] years. Surgical repair was performed in 33/49 (67.3%) at 1.5 ± 0.48 years; 14/33 (42.4%) were operated in the neonatal period and 18/33 (54.5%) within the first year. A percutaneous approach was used in 16/49 (32.7%), including 10 (20.4%) balloon angioplasties at 4.7 ± 0.7 years and 6 (12.2%) stents at 20.0 ± 3.2 years. The corrected Doppler isthmic gradient at last follow-up averaged 14.5 ± 8.0 mmHg. Hypertension was present in 16/49 (32.7%), with 12 (24.5%) on one drug and 4 (8.2%) on two.

OCTA findings

In the AoCo group, SCP VD was significantly lower compared to controls (38.32% versus 39.53%, p = 0.003). This decrease remained independent of age, sex, systolic BP, and axial length according to multivariable regression analysis (β = –1.32; 95% CI = –2.29 to –0.34; p = 0.009). Age was also inversely associated with VD (β = –0.07; p = 0.005), whereas other covariates showed no significant relationship. The model accounted for 24% of the variability in VD (R^2=0.24; p < 0.001). Model assumptions are presented in Supplementary Results (Section 3, Figures S2, S3 and S4). Additional OCTA parameters, including VLD, FD, and TVL, corroborated this pattern but these parameters were highly collinear with VD (ρ > 0.90) and are shown in the Supplementary Results (Section 4, Table S2). The effect size remained consistent after excluding systolic BP from the model (β = –1.32; p = 0.005), indicating that the observed microvascular rarefaction in AoCo is independent of current BP levels (Supplementary Results, Section 5, Table S3 and S4). FAZ parameters did not differ significantly between groups (Table 1).

CVI findings

CVI was significantly lower in AoCo patients (0.47 ± 0.03 vs 0.48 ± 0.02, p = 0.026).

Tortuosity findings

Retinal vessel tortuosity was increased in patients with AoCo. No significant differences were observed with TWIG 8; however, differences reached statistical significance with TWIG 30 (1.178 ± 0.018 vs 1.171 ± 0.015, p = 0.038). Additionally, artificial intelligence-based evaluation using infrared imaging also showed greater tortuosity in AoCo cases (distribution 17/8/24 vs 33/6/10, p = 0.004), with 32 out of 49

patients (65%) exhibiting moderate to severe tortuosity (Table 1). Both methods consistently identified increased tortuosity among individuals with AoCo patients.

Association with cardiovascular features and prognostic markers

Vessel density

SCP VD decreased progressively with increasing cardiovascular burden (Table 2). Compared to healthy controls, patients presenting with hypertension, residual gradient, LVH, and a non-dipping circadian BP pattern had significantly lower SCP VD (Table 2). VD was also diminished in patients with a 24-hour systolic BP load >25% and those with a hypertensive response to exercise. Conversely, AoCo patients without adverse markers (absence of hypertension, no significant gradient, no LVH, normal systolic load, and preserved dipping BP pattern) showed a milder reduction in VD. These exploratory subgroup comparisons, supported by trend analyses, are hypothesis-generating given the limited numbers in some strata, but are consistent with a graded microvascular phenotype in postoperative AoCo patients, even in the absence of overt complications or clinical risk markers.

Notably, median VD was lower in patients who underwent neonatal intervention compared to those treated later in life, despite fewer clinical burden markers (Table S5, Supplementary Results).

Vessel Tortuosity

Infrared-assessed retinal tortuosity increased with cardiovascular burden across various clinical subgroups. Ordered-logistic tests were significant for hypertension (χ^2=13.03, p=0.0015), isthmic residual gradient (χ^2=12.75, p=0.0017), LVH (χ^2=11.51, p=0.0032), circadian BP pattern (χ^2=15.41, p=0.0004), 24-hour systolic load (χ^2=10.72, p=0.0047), and hypertensive response to exercise (χ^2=11.08 p=0.0039).

Compared to controls, the probability of severe tortuosity (grade 2) was higher in patients with hypertension (p=0.001), high isthmic residual gradient (p=0.001), non-dipping circadian pattern (p=0.001), and hypertensive response to exercise (p=0.040). Tortuosity **also increased** with 24-hour systolic load > 25% (grade-2: 0.46 vs 0.20, p=0.010).

Even AoCo patients without adverse clinical markers already differed from controls: hypertension negative (p=0.017), no residual gradient (p=0.009), no LVH (p=0.003), dippers (p=0.004), and no hypertensive response to exercise (p=0.001), indicating a graded microvascular phenotype in AoCo despite anatomic repair.

Tortuosity **varied according to repair timing** (χ^2=14.82, p=0.0006). Compared to controls, patients repaired later in life **had a higher probability** of severe tortuosity (Pr grade-2=0.58 versus 0.20, p<0.001), whereas those repaired neonatally **did not differ significantly from controls** (Pr grade-2=0.28 versus 0.20, p=0.469).

Choroidal vascularity index

CVI was lower in AoCo group compared to controls (Table 1). CVI **showed limited and inconsistent variability** across AoCo subgroups. In contrast to vessel density, reductions in CVI did not follow the gradient of cardiovascular burden: lower CVI reached significance in some lower-risk subgroups (dippers, patients without a hypertensive exercise response, and those with a systolic BP load ≤25%) but not in their higher-risk counterparts. Given this lack of a coherent dose–response pattern and the exploratory nature of these comparisons, the CVI subgroup associations should be interpreted with caution; full subgroup results are provided in the Supplementary Results.

Discussion

AoCo is increasingly recognised as a **diffuse vascular disorder** rather than a localised narrowing of the aortic arch [20] . Even after repair, many patients show vascular changes such as increased stiffness and endothelial dysfunction [21,22], often subclinical yet linked to lifelong hypertension and cerebrovascular risk [1]. This persistent vascular phenotype is closely linked to chronic alterations in blood pressure regulation, positioning repaired AoCo within the spectrum of hypertensive cardiovascular disease.

Our study extends these observations to the retina, demonstrating a reduction in VD within the SCP independent of age, sex, axial length, and current BP. **This is the first multimodal ophthalmic imaging study in repaired AoCo**, highlighting the potential of retinal imaging to quantify systemic microvascular involvement. This supports the concept of **primary microvascular involvement in AoCo,** beyond residual haemodynamic load. Retinal vessel tortuosity was also increased, particularly in larger vessels, a feature previously documented in AoCo [23] and associated with vascular stress and remodelling [24] In addition, the choroidal vascularity index (CVI) was reduced, indicating **impaired choroidal vascular regulation**, as previously reported in cardiovascular disease [18]

Microvascular rarefaction and tortuosity were most pronounced in patients with hypertension, residual gradient, LVH, non-dipping profile, or hypertensive response to exercise (Table 2). Importantly, these alterations were also present in young, well-treated patients without overt clinical abnormalities**, suggesting subclinical vascular dysfunction similar to that reported in systemic hypertension** [18] AoCo patients without hypertension or other adverse markers still exhibited reduced VD, supporting a persistent microvascular phenotype beyond anatomical repair.

The progressive deterioration of retinal and choroidal biomarkers with increasing cardiovascular burden supports their role as early indicators of disease severity, potentially preceding overt hypertension or clinical events[25,26]. These findings are relevant, as many repaired AoCo patients require reintervention by midlife [27]. Ophthalmic biomarkers may refine risk stratification.

Our findings also shed light on the **impact of treatment timing and era.** Earlier studies reported tortuosity in up to 98% of adults with AoCo[23], decreasing with age post-repair whereas others found ~50%

prevalence [28]. **In our contemporary cohort**, treated earlier in life, 65% still showed moderate-to-severe tortuosity at a mean age of 22 years, **underscoring persistent microvascular involvement despite modern management.**

Of note, **patients repaired in the neonatal period showed tortuosity within the range of controls, while vessel density tended to be lower**, in contrast to the increased tortuosity seen in late-repaired patients (Tables 2 and 3); given the small neonatal subgroup (n=14), this observation is exploratory. It may reflect different vascular responses: late repair allows prolonged exposure to abnormal haemodynamics, favouring remodelling and tortuosity, whereas early repair **may limit remodelling but induce capillary loss secondary to developmental hypoperfusion.** Such early insults are frequent in severe neonatal coarctation, particularly when undiagnosed prenatally[21]. These hypotheses require confirmation in larger cohorts before tortuosity and density can be regarded as distinct, timing-dependent markers.

Quantitative retinal and choroidal imaging positions AoCo within the broader oculomics paradigm. The field of oculomics has established that detailed eye imaging can offer new insights into systemic health, predicting conditions such as hypertension, coronary artery disease, stroke risk, and cognitive decline[29]. Our study is the first to apply multimodal oculomics to AoCo, identifying a **retinal and choroidal signature of long-term vascular dysfunction** even in normotensive, well-corrected patients. Although OCTA differences were modest, their **potential for early risk detection is considerable**, particularly in identifying patients with elevated BP below diagnostic thresholds. **Future studies should longitudinally follow these cohorts,** linking retinal and choroidal biomarkers to cardiovascular outcomes, and **explore these features at the earliest stages of disease.** As repair strategies increasingly target infancy, understanding microvascular trajectories could **improve early cardiovascular risk assessment** and help identify higher-risk phenotype[30] As OCTA becomes more accessible, retinal microvascular analysis could enhance risk prediction and individualised care.

Our study has limitations. The between-group differences in retinal and choroidal metrics, although statistically significant and internally consistent, were modest in absolute terms and showed considerable overlap between groups, so their individual discriminative value at the patient level remains to be established. OCTA analysis was limited to high-quality scans, possibly causing selection bias. The modest sample size of this young, treated cohort limits subgroup power and generalisability. A proportion of patients were under antihypertensive therapy, **which may partially confound vascular differences.** Larger multicentre studies including treated and untreated individuals are warranted. **Normative OCTA thresholds remain undefined**, limiting immediate clinical applicability. Finally, the cross-sectional design precludes causal inference; longitudinal studies are needed to determine prognostic significance.

In summary, patients with AoCo exhibit ongoing microvascular changes, particularly a decreased retinal VD, closely associated with markers of cardiovascular burden. These findings support retinal microvascular metrics as non-invasive markers of hypertensive burden and systemic vascular remodelling in repaired AoCo.

Abbreviations

- AoCo – Aortic coarctation
- ABPM – Ambulatory blood pressure monitoring
- AI – Artificial intelligence
- ART – Automatic real-time averaging
- BMI – Body mass index
- BP – Blood pressure
- CI – Confidence interval
- CVI – Choroidal vascularity index
- DCP – Deep capillary plexus
- EDI – Enhanced depth imaging
- FAZ – Foveal avascular zone
- FD – Fractal dimension
- HR – High resolution
- HT – Hypertension / Hypertensive
- IOP – Intraocular pressure
- IQR – Interquartile range
- LVH – Left ventricular hypertrophy
- LVMI – Left ventricular mass index
- OCT – Optical coherence tomography
- OCTA – Optical coherence tomography angiography
- OD – Oculus dexter (right eye)
- SCP – Superficial capillary plexus
- SD – Standard deviation
- TVL – Total vessel length
- VLD – Vessel length density
- VD – Vessel density

Declarations

Conflict of interest

The authors declare no conflicts of interest related to this work.

Patient and Public Involvement

Patients or members of the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Funding

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgements

The authors thank the Orthoptics and Cardiology teams at Hospital Cuf Descobertas and ULSLO for their collaboration in patient recruitment and imaging acquisition. The authors are also grateful to all study participants for their involvement and commitment.

References

1. Salciccioli KB, Zachariah JP. Coarctation of the Aorta: Modern Paradigms Across the Lifespan. *Hypertension* 2023;80(10):1970–9. https://doi.org/10.1161/HYPERTENSIONAHA.123.19454/ASSET/0ED01D16-7988-481F-A709-317C1CCA6072/ASSETS/GRAPHIC/HYPERTENSIONAHA.123.19454.FIG06.JPG.
2. Toro-Salazar OH, Steinberger J, Thomas W *et al.* Long-term follow-up of patients after coarctation of the aorta repair. *American Journal of Cardiology* 2002;89(5):541–7. https://doi.org/10.1016/S0002-9149(01)02293-7.
3. Liew G, Wang JJ, Mitchell P *et al.* Retinal Vascular Imaging: A New Tool in Microvascular Disease Research. *Circ Cardiovasc Imaging* 2008;1(2):156–61. https://doi.org/10.1161/CIRCIMAGING.108.784876.
4. Monteiro-Henriques I, Rocha-Sousa A, Barbosa-Breda J. Optical coherence tomography angiography changes in cardiovascular systemic diseases and risk factors: A review. *Acta Ophthalmol* 2022;100(1):e1–e15. https://doi.org/10.1111/aos.14851.
5. Spaide RF, Fujimoto JG, Waheed NK *et al.* Optical coherence tomography angiography. *Prog Retin Eye Res* 2018;64:1–55. https://doi.org/10.1016/j.preteyeres.2017.11.003.
6. Aldousany AW, DiSessa TG, Alpert BS *et al.* Significance of the Doppler-derived gradient across a residual aortic coarctation. *Pediatr Cardiol* 1990;11(1):8–14. https://doi.org/10.1007/BF02239541.
7. McEvoy JW, McCarthy CP, Bruno RM *et al.* 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J* 2024;45(38):3912–4018. https://doi.org/10.1093/eurheartj/ehae178.
8. Lurbe E, Agabiti-Rosei E, Cruickshank JK *et al.* 2016 European Society ofHypertension guidelines for themanagement of high blood pressure in children and adolescents. *J Hypertens*

2016;34(10):1887–920. https://doi.org/10.1097/HJH.0000000000001039.

9. Conkar S, Ylmaz E, Hackara Ş *et al.* Is Daytime Systolic Load an Important Risk Factor for Target Organ Damage in Pediatric Hypertension? *J Clin Hypertens* 2015;17(10):760–6. https://doi.org/10.1111/jch.12608.
10. O'Brien E, White WB, Parati G *et al.* Ambulatory blood pressure monitoring in the 21st century. *J Clin Hypertens* 2018;20(7):1108–11. https://doi.org/10.1111/jch.13275.
11. Lang RM, Badano LP, Mor-Avi V *et al.* Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the ASE and the EACVI. *Eur Heart J Cardiovasc Imaging* 2015;16(3):233–70. https://doi.org/10.1093/ehjci/jev014.
12. Clarke MM, Zannino D, Stewart NP *et al.* Normative blood pressure response to exercise stress testing in children and adolescents. *Open Heart* 2021;8(2). https://doi.org/10.1136/OPENHRT-2021-001807.
13. Ghidoni C, Kruzik M, Rossi VA *et al.* Definitions for Hypertensive Response to Exercise. *Cardiol Rev* 2024;32(3):273–8. https://doi.org/10.1097/CRD.0000000000000506.
14. Untracht GR, Matos R, Dikaios N *et al. OCTAVA: An Open-Source Toolbox for Quantitative Analysis of Optical Coherence Tomography Angiography Images*. PLoS One 2021;16(12):e0261052. https://doi.org/10.1371/journal.pone.0261052.
15. Flores R, Carneiro Â, Neri G *et al.* Choroidal Vascular Impairment in Intermediate Age-Related Macular Degeneration. *Diagnostics* 2022;12(5). https://doi.org/10.3390/diagnostics12051290.
16. Untracht GR, Durkee MS, Zhao M *et al.* Towards standardising retinal OCT angiography image analysis with open-source toolbox OCTAVA. *Sci Rep* 2024;14(1). https://doi.org/10.1038/s41598-024-53501-6.
17. Sousa H. Characterization and Assessment of Vessel Tortuosity in Retinal Images. Faculty of Engineering of the University of Porto, Porto, Portugal;, 2024. https://hdl.handle.net/10216/162518 (13 Oct. 2025, date last accessed).
18. Anjos R, Ferreira A, Barkoudah E *et al.* Application of Optical Coherence Tomography Angiography Macular Analysis for Systemic Hypertension: A Systematic Review and Meta-analysis. *Am J Hypertens* 2022;35(4):356–64. https://doi.org/10.1093/ajh/hpab190.
19. Corvi F, Pellegrini M, Erba S *et al.* Reproducibility of Vessel Density, Fractal Dimension, and Foveal Avascular Zone Using 7 Different Optical Coherence Tomography Angiography Devices. *Am J Ophthalmol* 2018;186:25–31. https://doi.org/10.1016/j.ajo.2017.11.011.
20. Martins JD, Zachariah J, Tierney ESS *et al.* Impact of treatment modality on vascular function in coarctation of the aorta: The LOVE-COARCT study. *J Am Heart Assoc* 2019;8(7). https://doi.org/10.1161/JAHA.118.011536,.
21. Egbe AC, Miranda WR, Devara J *et al.* Effect of Combined Ventricular-Arterial Stiffening on Exercise Hemodynamics in Adults With Repaired Coarctation of Aorta. *CJC Open* 2021;3(5):603–8. https://doi.org/10.1016/j.cjco.2021.01.001.

22. Brili S, Tousoulis D, Antoniades C *et al.* Evidence of vascular dysfunction in young patients with successfully repaired coarctation of aorta. *Atherosclerosis* 2005;182(1):97–103. https://doi.org/10.1016/j.atherosclerosis.2005.01.030.
23. Gloan L Le, Chakor H, Mercier LA *et al.* Aortic coarctation and the retinal microvasculature. *Int J Cardiol* 2014;174(1):25–30. https://doi.org/10.1016/J.IJCARD.2014.03.129.
24. Schiffrin EL. Vascular remodeling in hypertension: mechanisms and treatment. *Hypertension* 2012;59(2):367–74. https://doi.org/10.1161/HYPERTENSIONAHA.111.187021.
25. Cibrão-Pedroso A, Rocha-Neves J, Vieira R *et al.* Changes in retinal and choroidal thickness after carotid endarterectomy: a systematic review. *Int J Retina Vitreous* 2025;11(1). https://doi.org/10.1186/s40942-025-00713-1.
26. Lemos M, Rato J, Mata MF da *et al.* Diastolic Function and Left Atrial Strain in Young Patients with History of Aortic Coarctation Repair. *Pediatr Cardiol* 2023;44(3):674–80. https://doi.org/10.1007/s00246-022-02992-z.
27. Lee MGY, Babu-Narayan S V., Kempny A *et al.* Long-term mortality and cardiovascular burden for adult survivors of coarctation of the aorta. *Heart* 2019;105(15):1190–6. https://doi.org/10.1136/HEARTJNL-2018-314257.
28. Johns KJ, Johns JA, Feman SS. Retinal Vascular Abnormalities in Patients with Coarctation of the Aorta. *Archives of Ophthalmology* 1991;109(9):1266–8. https://doi.org/10.1001/ARCHOPHT.1991.01080090090029,.
29. Poplin R, Varadarajan A V, Blumer K *et al.* Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. *Nat Biomed Eng* 2018;2(3):158–64. https://doi.org/10.1038/s41551-018-0195-0.
30. Weismann CG, Maretic A, Grell BS *et al.* Multimodal assessment of vascular and ventricular function in children and adults with repaired aortic coarctation. *Int J Cardiol* 2021;323:47–53. https://doi.org/10.1016/j.ijcard.2020.08.095.

Tables

Table 1. Clinical and ocular characteristics of the study population. Values are presented as mean ± standard deviation or median [IQR].

Variable	Controls	AoCo patients	p-value
	n =49	n =49	
Age, years	21.67 ± 8.44	21.12 ± 8.32	0.714
Sex, male (%)	51.0%	67.3%	0.100
Systolic BP, mmHg	119 ± 11.87	126.94 ± 17.24	0.009
Diastolic BP, mmHg	71.86 ± 8.03	75.06 ± 10.27	0.089
IOP, mmHg	15.95 ± 2.37 (n=48)	16.43 ± 2.87 (n=48)	0.369
Ocular axial length, mm	23.56 ± 0.92	23.33 ± 1.31	0.332
OCTA			
Vessel density (%)	39.53 [38.87; 40.06] (n=39)	38.32 [35.65; 39.47] (n=39)	0.003
Vessel length density (%)	7.22 ± 0.37 (n=39)	6.89 ± 0.58 (n=39)	0.004
Fractal dimension [1]	1.65 ± 0.01 (n=39)	1.64 ± 0.01 (n=39)	0.005
Total vessel length [µm]	207.79 ± 14.91 (n=39)	197.99 ± 22.45 (n=39)	0.026
Mean vessel diameter [µm]	17.58 ± 0.78 (n=39)	17.50 ± 1.00 (n=39)	0.699
FAZ area (mm^2)	0.63 ± 0.14 (n=39)	0.67 ± 0.24 (n=39)	0.329
FAZ perimeter (mm)	6.37 ± 1.25 (n=39)	6.44 ± 1.74 (n=39)	0.832
FAZ acircularity index	2.28 ± 0.32 (n = 39)	2.24 ± 0.32 (n = 39)	0.656
Choroid			
CVI	0.480 ± 0.02 (n=47)	0.468 ± 0.03 (n=49)	0.026
Vessel Tortuosity			
Vessel tortuosity (TWIG8) [1]	1.139 ± 0.010 (n=39)	1.142 ± 0.009 (n=39)	0.195
Vessel tortuosity (TWIG30) [1]	1.171 ± 0.015 (n=39)	1.178 ± 0.018 (n=39)	0.038
IR Tortuosity (0/1/2)	33 / 6 / 10	17/08/24	0.004

Table 1. Values are presented as median [IQR] or mean ± SD, based on data distribution. Vessel density and microvascular metrics were obtained from 3×3 mm optical coherence tomography angiography (OCTA) scans centered on the fovea. Measures of the foveal avascular zone (FAZ) included area, perimeter, and acircularity index. The choroidal vascularity index (CVI) was calculated from binarized subfoveal enhanced depth imaging optical coherence tomography (EDI-OCT) images. Tortuosity was evaluated utilizing two automated methods (TWIG 8 and TWIG 30), and en face IR infrared tortuosity was

graded on a scale: 0 indicating low, 1 moderate, and 2 marked. Statistical significance was defined as $p < 0.05$. [1] is dimensionless.

Abbreviations: AoCo, aortic coarctation; BP, blood pressure; CVI, choroidal vascularity index; EDI, enhanced depth imaging; FAZ, foveal avascular zone; IOP, intraocular pressure; IQR, interquartile range; IR, infrared; OCTA, optical coherence tomography angiography; SD, standard deviation.

Table 2. Retinal vessel density in controls versus AoCo patients across clinical subgroups with or without adverse prognostic markers.

Adverse markers	Group 1 Controls Vessel density (%)	Group 2 No adverse marker Vessel density (%)	Group 3 With adverse marker Vessel density (%)	KW / Trend
Hypertension Group 1 = Control Group 2 = AoCo no HT Group 3 = AoCo with HT	39.53 [38.87-40.07] (n=39)	38.57 [35.70–39.48] (n=26) †p = 0.018	37.05 [35.50–39.11] (n=13) ‡p = 0.010	KW p = 0.009 trend p = 0.003
Isthmic residual gradient 1 = Control 2 = AoCo gradient < 20mmHg 3 = AoCo gradient > 20mmHg	39.53 [38.87–40.07] (n=39)	38.49 [36.38–39.47] (n=30) †p = 0.009	36.76 [35.12–40.00] (n=9) ‡p = 0.033	KW p = 0.010 trend p = 0.004
LV hypertrophy 1 = Control 2 = AoCo without LVH 3 = AoCo with LVH	39.53 [38.87–40.07] (n=39)	38.38 [36.17–39.52] (n=33) †p = 0.023	35.87 [34.38–38.65] (n=6) ‡p = 0.001	KW p = 0.002 trend p = 0.001
BP circadian pattern 1 = Control 2 = AoCo dipper 3 = AoCo non-dipper	39.53 [38.87–40.07] (n=39)	38.60 [36.76–39.47] (n=27) †p = 0.019	34.43 [33.35–39.17] (n=5) ‡p = 0.031	KW p < 0.01 trend p < 0.01
24 h systolic load on ABPM 1 = Control 2 = AoCo with load ≤25% 3 = AoCo with load >25%	39.53 [38.87–40.07] (n=39)	38.82 [37.23–39.98] (n=21) †p = 0.175	37.04 [34.95–38.77] (n=18) ‡p = <0.001	KW p = 0.001
Exercise hypertensive response 1 = Control	39.53 [38.87–40.07] (n=39)	38.8 [34.98–41.13] (n=23) †p = 0.155	37.66 [35.43–38.55] (n=16) ‡p = <0.001	KW p = 0.003

2 = AoCo without HT response 3 = AoCo with HT response				
Timing of intervention 1 = Control 2 = AoCo neonatal repair 3 = AoCo late treatment	39.53 [38.87–40.07] (n=39)	37.71 [36.58–38.85] (n=13) †p = 0.004	38.46 [35.47–39.76] (n=26) ‡p = 0.026	KW p = 0.009

Legend: Data are presented as medians with interquartile ranges [IQR], accompanied by the number of observations per group (n). Group 1 comprises controls; Group 2 consists of AoCo without adverse markers; Group 3 includes AoCo with adverse markers. †p-value indicates comparison between Group 2 and controls; ‡p-value indicates comparison between Group 3 and controls.

Abbreviations: ABPM, ambulatory blood pressure monitoring; AoCo, aortic coarctation; BP, blood pressure; HT, hypertensive; IQR, interquartile range; KW p, Kruskal–Wallis test; LVH, left ventricular hypertrophy; Trend p, non-parametric trend test (Cuzick's non-parametric test).

Table 3. Vessel tortuosity in controls versus AoCo patients across clinical subgroups with or without adverse prognostic markers.

Adverse markers	Group 1 Controls **Vessel tortuosity**	Group 2 No adverse marker **Vessel tortuosity**	Group 3 With adverse marker **Vessel tortuosity**	$\chi^2(2)$; p value
Hypertension Group 1 = Control, Group 2 = AoCo no HT Group 3 = AoCo with HT	Pr(0/1/2) = 0.67 / 0.13 / 0.20 n=49	Pr(0/1/2) = 0.40 / 0.16 / 0.43 † p=0.017 n=33	Pr(0/1/2) = 0.26 / 0.15 / 0.60 ‡ p=0.001 n=16	$\chi^2(2)=13.03$; p=0.0015
Isthmic residual gradient 1 = Control 2 = AoCo gradient < 20mmHg 3 = AoCo gradient > 20mmHg	Pr(0/1/2) = 0.67 / 0.13 / 0.20 n=49	Pr(0/1/2) = 0.39 / 0.17 / 0.44 † p=0.009 n=37	Pr(0/1/2) = 0.24 / 0.14 / 0.62 ‡ p=0.001 n=9	$\chi^2(2)=12.75$; p=0.0017
LV hypertrophy 1 = Control 2 = AoCo without LVH 3 = AoCo with LVH	Pr(0/1/2) = 0.67 / 0.13 / 0.20 n=49	Pr(0/1/2) = 0.36 / 0.16 / 0.48 † p=0.003 n=43	Pr(0/1/2) = 0.28 / 0.15 / 0.57 ‡ p=0.015 n=6	$\chi^2(2)=11.51$; p=0.0032
BP circadian pattern 1 = Control 2 = AoCo dipper 3 = AoCo non-dipper	Pr(0/1/2) = 0.67 / 0.14 / 0.19 n=49	Pr(0/1/2) = 0.35 / 0.18 / 0.47 † p=0.004 n=32	Pr(0/1/2) = 0.16 / 0.12 / 0.72 ‡ p=0.001 n=10	$\chi^2(2)=15.41$; p=0.0004
Systolic load on ABPM 1 = Control 2 = AoCo with load ≤25% 3 = AoCo with load >25%	Pr(0/1/2) = 0.67 / 0.13 / 0.20 n=49	Pr(0/1/2) = 0.32 / 0.16 / 0.52 † p=0.004 n=26	Pr(0/1/2)= 0.38 / 0.16 / 0.46 ‡ p=0.010 n=23	$\chi^2(2)=10.72$; p=0.0047

Exercise hypertensive response 1 = Control 2 = AoCo no HT response 3 = AoCo with HT response	Pr(0/1/2) = 0.67 / 0.13 / 0.20 n=49	Pr(0/1/2) = 0.31 / 0.16 / 0.54 † p=0.001 n=21	Pr(0/1/2)= 0.42 / 0.16/ 0.42 ‡ p=0.040 n=28	$\chi^2(2)=11.08$; p=0.0039
Timing of intervention 1 = Control 2 = AoCo neonatal repair 3 = AoCo late treatment	Pr(0/1/2) = 0.67 / 0.13 / 0.20 n = 49	Pr(0/1/2) = 0.57 / 0.16 / 0.28 † p = 0.469 n = 14	Pr(0/1/2) = 0.27 / 0.15 / 0.58 ‡ p < 0.001 n = 35	$\chi^2(2) = 14.82$ p = 0.0006

Legend: Values are predicted probabilities derived from ordered logistic regression (ologit) for categories of vessel tortuosity (0 = none, 1 = moderate, 2 = severe), rounded to two decimal places. The symbols † and ‡ denote p-values for the pairwise comparison of each AoCo subgroup against the control group, obtained from the ordered logistic regression coefficients (group versus control). The 'global' column reports the Wald χ^2 statistic with 2 degrees of freedom and the corresponding p-value, based on the overall ordinal logistic regression model. Group 1 corresponds to controls; Group 2 comprises individuals with AoCo without adverse markers; Group 3 includes individuals with AoCo with adverse markers. Abbreviations: ABPM, ambulatory blood pressure monitoring; AoCo, aortic coarctation; BP, blood pressure; HT, hypertensive; LVH, left ventricular hypertrophy

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMethods.docx
- graphicalabstract.pptx
- SupplementaryResults.docx