Retinal Nerve Fiber Layer in Aortic Coarctation Patients

Análise da Camada de Fibras Nervosas da Retina em Doentes com Coartação da Aorta

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Recebido/Received: 2023-10-15 | **Aceite/Accepted:** 2024-06-23 | **Published online/Publicado online:** 2024-11-19

DOI: https://doi.org/10.48560/rspo.33098

ABSTRACT

INTRODUCTION: Aortic coarctation (COA) is a congenital cardiovascular defect characterized by a narrowed aorta, leading to increased afterload and significant hypertension. COA is associated with severe vascular complications, including coronary atherosclerosis, cerebrovascular accidents, and sudden death. Given the link between retinal microvascular changes and cerebrovascular disease and considering the shared embryological development between the brain and heart in congenital cardiac disease, we can observe vascular lesions caused by COA through transneural degeneration. Detecting and monitoring related-vascular damage in COA patients is crucial to prevent these complications. Notably, the retinal nerve fiber layer (RNFL) shows promising potential as a non-invasive biomarker, providing insights into COA patients' vascular health.

Our purpose was to evaluate alterations in RNFL thickness in COA patients using spectral-domain optical coherence tomography (SD-OCT).

METHODS: Prospective data were collected from patients diagnosed with COA and healthy controls. SD-OCT was performed to measure peripapillary RNFL in both eyes of each patient.

RESULTS: Forty-eight patients with COA diagnosis (COA group; mean [SD] age, 21.0 [8.4] years; 32 males [67%]) and 48 healthy normal controls (control group; mean [SD] age, 21.4 [8.8] years; 23 males [49%]) were included in this study. In univariate analysis, peripapillary RNFL thickness was reduced in both eyes in the COA group compared with the control group in the global parameter (OD, $p = 0.058$; OS, $p = 0.036$), superior-nasal (OD, $p = 0.006$; OS, $p = 0.006$), and superior-temporal (OD, $p = 0.023$; OS, $p = 0.085$). In multivariate logistic regression analysis, only the supero-nasal sector in both eyes showed a significant reduction in peripapillary RNFL thickness on COA group (right eye: coef = 12.83 Std err = 4.44, p-value = 0.005, 95% CI = [4.00 – 21.66]; left eye: coef = 12.80, Std err = 4.16, p-value = 0.003, 95% CI = [4.54 – 21.07]) after adjusting for age, male sex, blood pressure, and IOP.

CONCLUSION: These findings suggest that COA patients might exhibit significant alterations in RNFL thickness, particularly in specific sectors, indicating potential neurological reper-

cussions. Such insights could have valuable implications for the early detection and management of COA-related vascular complications, potentially serving as a non-invasive biomarker.

KEYWORDS: Aortic Coarctation; Biomarkers; Nerve Fibers; Retinal Diseases; Retinal Vessels.

RESUMO

INTRODUÇÃO: A coarctação da aorta (COA) é um defeito cardiovascular congénito definido como um estreitamento na aorta, que provoca aumento da pós-carga e hipertensão. A COA está associada a complicações vasculares, incluindo aterosclerose coronária, acidentes cerebrovasculares e morte súbita. Dada a ligação entre alterações microvasculares da retina e doença cerebrovascular, podemos observar lesões vasculares causadas pela COA através do processo de degeneração transneural. A deteção e monitorização de danos vasculares relacionados com COA é crucial para prevenir estas complicações. A *retinal nerve fiber layer* (RNFL) mostra potencial como biomarcador não-invasivo, fornecendo informações sobre a saúde vascular dos doentes com COA.

O nosso objetivo foi avaliar alterações na espessura da RNFL em doentes com COA através da tomografia de coerência ótica de domínio espectral (SD-OCT).

MÉTODOS: Prospetivamente, os dados foram colhidos de participantes com diagnóstico de COA e de controlos saudáveis. SD-OCT foi realizado para medir a RNFL peripapilar em ambos os olhos de cada participante.

RESULTADOS: Quarenta e oito participantes com diagnóstico de COA (idade média [DP], 21,0 [8,4] anos; 32 homens [67%]) e 48 controlos normais saudáveis (grupo controlo; idade média [DP], 21,4 [8,8] anos; 23 homens [49%]) foram incluídos. Na análise univariada, a espessura da RNFL encontra-se reduzida em ambos os olhos no grupo COA no parâmetro global (OD, p = 0,058; OS, p = 0,036) , nasal-superior (OD, p = 0,006; OS, p = 0,006) e temporal-superior (OD, p = 0,023; OS, p = 0,085). Na regressão logistíca multivariada, apenas o setor supero-nasal apresenta redução na RNFL após ajuste para idade, sexo, pressão arterial e PIO (OD: coef = 12,83 Std err = 4,44, p-value = 0,005, 95% IC = [4,00 – 21,66] ; OE: coef = 12,80, Std err = 4,16, p-value = 0,003, 95% IC = [4,54 – 21,07]).

CONCLUSÃO: Estes resultados sugerem que doentes com COA apresentam alterações da RFNL, particularmente em setores específicos, indicando potenciais repercussões neurológicas. Tais insights podem ter implicações para a deteção precoce e abordagem de complicações vasculares relacionadas à COA, servindo potencialmente como um biomarcador não-invasivo.

PALAVRAS-CHAVE: Biomarcadores; Coartação da Aorta; Doenças da Retina; Fibras Nervosas; Vasos Retinianos.

INTRODUCTION

Aortic coarctation (COA) is a congenital cardiovascular disorder characterized by the narrowing of the thoracic aorta, typically occurring near the insertion point of the ductus arteriosus.[1] It presents a significant health concern affecting individuals of all age groups.[2] COA constitutes approximately 6% to 8% of all congenital heart diseases, with an incidence rate of 3 cases per 10 000 live births and a male-to-female ratio of 2:1.[1] COA represents a lifelong condition that often necessitates multiple interventions and continuous medical monitoring, imposing a substantial burden on affected individuals and the healthcare system.[1,2]

In this pathological condition, the narrowing of the aorta results in increased afterload, primarily affecting blood flow from the left ventricle.[1] Despite notable advancements in percutaneous interventions, surgical repair techniques, and medical therapies, the long-term prognosis for COA patients remains poor due to morbidity and excess mortality associated with vascular complications.[1,3,4] These complications encompass systemic arterial hypertension, accelerated coronary atherosclerosis, aortic dissection, aortic rupture, as well as cerebrovascular accidents and sudden death.[2,5–8] COA frequently leads to significant secondary hypertension in the aorta and the branch vessels proximal to the site of narrowing and causes physical changes in blood vessels, including thickening of the elastic lamina.[9,10]

The eye serves as an early indicator of the effects of el-

evated blood pressure, particularly through its ability to visualize changes in retinal microvasculature.[4,11] Numerous studies have reported a strong link between retinal microvascular changes and cerebrovascular disease.[12–14] In the Atherosclerosis Risk in Communities study, individuals with hypertensive retinopathy were at an increased risk of developing incident stroke and experienced cognitive decline, cerebral white matter lesions, and cerebral atrophy, even after controlling for traditional risk factors.[13]

Interestingly, the eye can also be affected in COA, with documented changes in the ocular vascular network.[4] Notable findings from studies include a distinctive microvascular pattern characterized by bilaterally symmetric tortuosity of retinal arteries and veins.[4] Moreover, these investigations have revealed a reduction in the ratio of arterial-to-venous (A/V) tortuosity scores, with higher scores associated with adverse vascular outcomes in patients aged 45 years or older.[4]

In the context of the shared embryological development between the brain and heart in congenital cardiac disease,[15,16] we can observe vascular lesions caused by COA through the transneural degeneration process.[17] This process involves the complex deterioration of nerve cells, either due to a direct insult to the cells themselves or disruptions in their connections.[17] Within the visual system, the degeneration of retinal ganglion cells, which are second-order neurons, typically follows damage to the posterior cortex, where third-order neurons are located.[17] Peripapillary retinal nerve fiber layer (RNFL) measurements have been employed to assess changes in ganglion cells in cases of posterior lesions.[18,19]

Detecting and monitoring vascular-related complications in COA patients is paramount in managing their long-term health and preventing such situations. However, the current methods for assessing vascular damage in these individuals primarily rely on invasive and often costly procedures, such as angiography or magnetic resonance imaging.[1]

Understanding and validating the potential significance of RNFL changes in COA patients could potentially revolutionize the monitoring of vascular health in this population, especially regarding potential neurological repercussions. If RNFL changes prove to be a reliable non-invasive biomarker, they could offer a simple, cost-effective alternative. This approach could pave the way for a more comprehensive understanding of the pathophysiology of COA and its late complications, ultimately enhancing patient management and follow-up care.

We hypothesize that vascular alterations in COA patients may be reflected in RNFL changes, shedding light on the pathophysiology of COA, particularly its complications in the eye and neurological field.

METHODS

STUDY DESIGN

A prospective observational study, titled COARTEYE, was conducted at the Ophthalmology Department of Hospital CUF Descobertas in Lisbon, Portugal. The Hospital's Ethics Committees approved the study and adhered to the principles of the 1964 Helsinki Declaration and its subsequent amendments or equivalent ethical standards. Informed consent was obtained from all participants before their inclusion in the study.

SAMPLE POPULATION

We recruited patients diagnosed with COA from the Pediatric Cardiology Department of Centro Hospitalar Lisboa Ocidental and CUF Descobertas between February 2020 and July 2023. The control group consisted of consecutive healthy volunteers without COA and had no ocular or systemic diseases.

Exclusion criteria included participants under 6 years old, those with a refractive error greater than 6 diopters of spherical equivalent, intraocular pressure (IOP) exceeding 24 mmHg, known concurrent ocular diseases, history of ocular trauma or previous ocular surgery, evidence of other neurological diseases affecting visual fields or retinal/optic disc imaging, and history of systemic diseases, except for known COA complications that might lead to vascular disease.

ENDPOINT

For the following subtopics of the methods we only present part of the COARTEYE, since the aim of this article is to assess RNFL thickness in COA patients using spectral-domain optical coherence tomography (SD-OCT).

DATA COLLECTION

The study involved a single visit to the Ophthalmology Department at Hospital CUF Descobertas, during which non-invasive scans routinely used in ophthalmology practice were performed. Each participant had a systemic and ophthalmological history review and a complete ophthalmological assessment. These procedures were conducted by two experienced orthoptists under consistent environmental conditions and included: a) peripheral arterial pressure and cardiac frequency measurements in the right arm and left arm, b) autorefractometry, c) biometry (axial length), d) tonometry (i-CARE per eye), e) optical coherence tomography (OCT) using the SD-OCT Spectralis Heidelberg®.

IMAGING

SD-OCT scans were performed by a single experienced technician masked to the patient's information using the Heidelberg Spectralis (Wavelength: 870 nm; Heidelberg Engineering Co., Heidelberg, Germany) without and with enhanced depth imaging (EDI). No optical correction was used during the scans and 1 drop of artificial tear was used to increase image quality. A 20° × 20° retinal region was scanned using a horizontal fast protocol (25 sections separated by 240 µm) centered on the fovea with an A-scan density of 1024. The peripapillary area was scanned by a circular scan with 12° in diameter centered in the optic disc with an A-scan density of 1536. Only images with a clear view of the different structures to be analyzed and a minimum of 20-dB resolution were ac-

cepted for study inclusion. The technician who performed the scans selected one image centered in the fovea and one centered in the optic disc. A Valsalva Maneuver was performed before one of the OCT scans with EDI. Automated peripapillary RNFL thickness measurements were generated using the Heidelberg Eye Explorer software provided by the manufacturer. Values of global RNFL thickness and nasal (N), superonasal (SN), inferonasal (IN), temporal (T), superotemporal (ST), and inferotemporal (IT) were collected (Fig. 1). Image J was used to analyze central macular thickness.

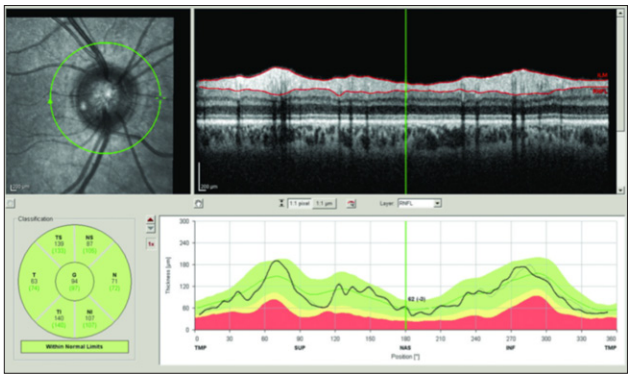

Figure 1. Example of the peri-papillary retinal nerve fiber layer (RNFL) circular scan centered on the optic nerve head (ONH) using Spectralis optic coherence tomography (OCT) in a control eye after applying the follow-up function. The graph on the lower right of the window presents the RNFL thickness detected along the circular scan (black curve), compared to values from the normative database (green curve). The black values in the pie chart (lower left) give the average RNFL thickness value for each sector as well as the global average (G).

N - nasal; T - temporal; TS - superior-temporal; TI - inferior-temporal; NS - superior-nasal; NI - inferior-nasal.

The reliability and reproducibility of measurements were ensured through quality control measures during image acquisition, including inter-observer and intra-observer variability assessments.

STATISTICAL ANALYSIS

Descriptive statistics for continuous variables are presented as the mean and standard deviation (SD) or as the median (interquartile range or range), depending on the distribution's skewness. Categorical variables are presented as the number (n) and percentage (%) of the total. The Shapiro-Wilk test and histogram were used to assess normality. The Mann-Whitney test was employed to determine the mean significance between groups and the Chi-squared test was used for categorical variables. The two-sample Wilcoxon rank-sum (Mann-Whitney) test was used to detect differences in RNFL thickness between the eyes of the same subject in the COA group. After univariate analysis, we proceeded to perform multivariable logistic regression using a backward elimination model to explore the correlation between clinical parameters and measurements of COA patients.

All statistical analyses were performed using Stata (version 16.1, StataCorp LLC, College Station, TX) and R Statistical Software (version 4.0.2; R Core Team 2020). All *p*-values resulted from two-sided tests, and results were considered statistically significant at $p < 0.05$.

RESULTS

For this study, a total of 96 patients met the inclusion criteria, comprising 48 patients diagnosed with COA (COA group) and 48 healthy controls (control group). Adequate image quality was obtained for at least one image in both eyes of all participants (96 eyes in the COA group and 96 eyes in the control group).

DEMOGRAPHIC ANDC LINICAL CHARACTERISTICS

We initially conducted a comparative analysis between COA patients and controls to characterize our study popu-

Table 1. Baseline characteristics.

Patient characteristics	COA group (n = 48)	Control group (n = 48)	*p* (two-sided)
Age (years; mean, SD)	21.0 (8.4)	21.4 (8.8)	0.900
Male (n,%)	32 (67%)	23 (48%)	0.063
Spherical equivalent (mean, SD)			
OD	-0.56 (1.6)	-0.64 (1.5)	0.752
OS	-0.62 (1.9)	-0.52 (1.3)	0.860
Axial length (mm; mean, SD)			
OD	23.56 (1.5)	23.56 (1.0)	0.864
OS	23.34 (1.4)	23.50 (1.0)	0.561
IOP (mmHg, mean, SD)			
OD	16 (2.9)	16 (2.3)	0.639
OS	16 (2.1)	16 (2.6)	0.642
Cardiac frequency (bpm; mean, SD)			
Right arm	73 (13.4)	70 (12.9)	0.933
Left arm	73 (13.6)	71 (12.2)	0.136
Central macular thickness (µm, mean, SD)			
OD	229 (19.6)	226 (14.9)	0.587
OS	230 (22.6)	226 (14.0)	0.991
DBP (mmHg; mean, SD)			
Right arm	75 (10.3)	72 (8.6)	0.073
Left arm	74 (11.5)	73 (9.2)	0.658
Mean	74 (10.2)	73 (8.4)	0.144
SBP (mmHg; mean, SD)			
Right arm	127 (17.1)	119 (12.5)	0.002*
Left arm	121 (14.7)	117 (11.9)	0.004*
Mean	124 (14.7)	115 (17.1)	0.014*

bpm beats per minute, DBP diastolic blood pressure, IOP intraocular pressure, mm millimeters, OD right eye, OS left eye, SBP systolic blood pressure, SD standard deviation. *p-value < 0.05

lation. Demographic and clinical characteristics are presented in Table 1.

There were no statistically significant differences observed in age or gender between the two groups (age: 21.0 ± 8.4 years in the COA group *vs* 21.4 ± 8.8 years in the control group, $p = 0.900$; gender: 32 males in the COA group *vs* 23 males in the control group, $p = 0.063$). However, it is worth noting that the COA group had a higher proportion of male participants.

With respect to blood pressure status, as expected, patients in the COA group exhibited statistically significant higher systolic blood pressure levels compared to the control group (SBP, right arm: $p = 0.002$; SBP, left arm: $p = 0.004$, mean SBP: $p = 0.014$).

PERIPAPILLARY RETINAL NERVE FIBRE THICKNESS

In univariate analysis, peripapillary RNFL thickness was found to be reduced in both eyes of the COA group when compared to the control group, as outlined in Table 2. The global peripapillary RNFL thickness was significantly reduced in the left eye of the COA group ($p = 0.036$), with a noticeable reduction in thickness, although not statistically significant, in the right eye ($p = 0.058$).

When compared to the control group, statistically significant thinning of the peripapillary RNFL was observed in the superior-nasal sector in both eyes (right eye: $p = 0.006$; left eye: $p = 0.006$) and in the superior-temporal sector in the right eye ($p = 0.023$), with a slight reduction in the left eye ($p = 0.085$). The temporal, nasal, inferior-nasal, and inferior-temporal sectors did not exhibit statistically significant reductions in RNFL thickness in either eye within the COA group.

In multivariate logistic regression analysis, only the supero-nasal sector in both eyes showed a significant reduction in peripapillary RNFL thickness on COA group (right eye: coef = 12.83 Std err = 4.44, p-value = 0.005, 95% CI = [4.00 – 21.66] ; left eye: coef = 12.80, Std err = 4.16, p-value = 0.003, 95% CI = [4.54 – 21.07]) after adjusting for age, sex, blood pressure, and IOP.

No difference was found in peripapillary RNFL thickness between both eyes of same subject in the COA group (Table 3).

Table 3. Peripapillary retinal nerve fibre thickness in COA group comparing OD *versus* OS.

RNFL thickness (µm; mean, SD)			
	COA group		
Sector	Right eye (n = 48)	Left eye (n = 48)	*p*
Global	100 (11.08)	98 (11.43)	0.284
ST	138 (19.45)	137 (19.77)	0.910
SN	107 (19.71)	113 (18.09)	0.383
T	69 (10.69)	68 (11.95)	0.734
N	80 (14.71)	75 (12.78)	0.241
IT	139 (21.71)	137 (22.09)	0.956
IN	117 (30.59)	114 (27.74)	0.291

G global, IN inferonasal, IT inferotemporal, N nasal, RNFL retinal never fiber layer, SD standard deviation, SN superonasal, ST superotemporal, T temporal.

DISCUSSION

This prospective observational study investigates the intricate relationship between COA and potential neuroretinal repercussions, as indicated by vascular-related damage assessed through peripapillary RNFL thickness.

The brain and the retina share similar anatomic features and physiological properties.[20] Patients with COA are susceptible to neurovascular complications,[21] with cerebrovascular disease being the most frequent cause of years of life lost (YLL).[22]

In our analysis, we identified reduced RNFL thickness in the COA group globally (right eye: $p = 0.058$; left eye: $p = 0.036$), particularly in the superior-nasal sector in both eyes ($p = 0.006$) and the superior-temporal sector (right eye: $p = 0.023$; left eye: $p = 0.085$). However, only the supero-nasal sector in both eyes showed a marked difference in multivariable logistic regression after adjusting for parameters such as age, sex, blood pressure and IOP. The notable reduction in peripapillary RNFL thickness, especially in specific eye sectors, suggests that COA patients may experience neurological involvement. This raises the question of whether COA itself contributes to RNFL thickness changes, or if these changes are primarily driven by vascular-related complications.

Table 2. Peripapillary retinal nerve fibre thickness in control and COA groups.

RNFL thickness (µm; mean, SD)						
	Right eye			Left eye		
Sector	COA group (n = 48)	Control group (n = 48)	*p*	COA group (n = 48)	Control group (n = 48)	*p*
Global	100 (11.08)	104 (9.08)	0.058	98 (11.43)	103 (9.31)	0.036*
ST	138 (19.45)	144 (21.56)	0.023*	137 (19.77)	144 (17.41)	0.085
SN	107 (19.71)	119 (21.61)	0.006*	113 (18.09)	128 (20.93)	0.006*
T	69 (10.69)	71 (10.64)	0.328	68 (11.95)	68 (9.88)	0.814
N	80 (14.71)	80 (15.39)	0.817	75 (12.78)	77 (14.20)	0.555
IT	139 (21.71)	146 (16.32)	0.062	137 (22.09)	143 (16.84)	0.068
IN	117 (30.59)	118 (29.97)	0.913	114 (27.74)	119 (24.98)	0.570

G global, IN inferonasal, IT inferotemporal, N nasal, RNFL retinal never fiber layer, SD standard deviation, SN superonasal, ST superotemporal, T temporal.
*p-value < 0.05.

The results of the present study are in agreement with the findings of previous investigations in which SD-OCT was applied to image the retina and to describe retinal changes, mainly in the RNFL of patients with Alzheimer disease, Parkinson disease, or schizophrenia.[23–25] It suggests that SD-OCT may be added to the retinal imaging diagnostic tests in patients with neurological conditions.

A study by Wang and colleagues involving 154 patients with acute ischemic stroke and 2890 subjects from the population-based Beijing Eye Study as a control group found that acute stroke was significantly associated with RNFL thinning ($p < 0.001$; odds OR: 6.23) 26. In an investigation by Kim and associates of 4395 Korean individuals undergoing health check-up examinations, a higher prevalence of RNFL thinning was significantly correlated with cerebral small vessel diseases as detected by magnetic resonance imaging.[27] Other studies have shown associations between cerebrovascular diseases and retinal microvascular abnormalities, such as localized and generalized arteriolar thinning, arterio-venous nicking, and a lower arteriolar/venular diameter ratio.[13,28–30]

As seen in a mouse eye study with induced transverse aortic coarctation, the sustained elevation of blood pressure appears to exhaust the ability of blood flow regulation, possibly because of the impaired endothelial nitric oxide function and diminished microvascular resistance.[31] These vascular changes may subsequently lead to ocular hyperperfusion, oxidative stress, glial cell activation, and neuroretinal dysfunction, which precede the macroscopic structural changes in the retina.[31]

Histological studies have further unveiled the presence of vascular networks within the RNFL[32,33] which supply oxygen and nutrients to the neuroretinal layers, inevitably influencing RNFL thickness.[34] It is noteworthy that larger retinal vessels significantly contribute to peripapillary RNFL thickness, constituting approximately 13% of the total RNFL thickness.[35] Additionally, Xu *et al* found that localized RNFL defects were associated with arterial hypertension.[36] In that study, the authors presented patients with arterial hypertension and multiple localized RNFL defects located at 10, 11, and 12 o'clock.[36] A previous study reported that myopia and a small optic disc were related to multiple RNFL defects in glaucoma.[37] In our study, highly myopic eyes (spherical equivalent >−6 D) were excluded because atrophic changes of the neural retina and choroid could obscure a clear pattern of RNFL defects. Another study noted that split RNFL defects were more common in the superior quadrant.[38] Conversely, in glaucoma, localized RNFL defects are typically observed in the inferotemporal region, followed by the superotemporal region.[39–41] The strong association with systemic vascular disease seemed to play a role in the predominance of split RNFL defects in the superior sector of the optic disc.[38] These findings align with our results. Vascular insufficiency or disruptions in the optic nerve head may contribute to the increased prevalence of split RNFL defects at the superior side of the optic disc due to gravitational effects.[38] However, confirmatory studies are needed.

Despite the valuable insights gained from this study, several limitations need to be acknowledged. The study was conducted within the Portuguese population, and it remains uncertain whether the findings can be generalized to other ethnic groups. RNFL defects and retinal microvascular abnormalities can be associated with arterial blood pressure levels, arteriosclerosis, or other vascular issues, making it challenging to isolate the precise cause. Additionally, we did not evaluate dysfunction itself, as measured by visual acuity and visual field, or use advanced imaging techniques such as optical coherence tomography angiography (OCTA) to investigate changes in retinal microvasculature or neuroimaging to assess neurovascular changes. Moreover, the study provides a static snapshot and does not capture dynamic changes that may occur over time. Longitudinal studies tracking RNFL thickness are necessary to understand the progression of vascular alterations and their impact on neurological health in COA patients.

In conclusion, the findings of this study suggest that COA patients might exhibit significant alterations in peripapillary RNFL thickness, particularly in specific sectors, indicating potential neurological repercussions. These insights could have valuable implications for the early detection and management of COA-related vascular complications, potentially serving as a non-invasive biomarker. The study underscores the importance of ophthalmological assessments in the comprehensive care of COA patients, offering valuable insights into vascular health and neurological risks. Physicians could use simple, cost-effective eye examinations as part of routine care to monitor vascular health and detect early neurological risks. This challenges us to explore the intricate connections between cardiovascular and neurological health and underscores the importance of early detection and comprehensive care for COA patients.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

All authors declare that they had a substantial and direct intellectual contribution in the design and elaboration of this article, that they participated in the analysis and interpretation of the data, in the writing of the manuscript, in the revision of versions and critical revision of its content and in the approval of the final version.

Todos os autores declaram que tiveram uma contribuição intelectual substancial e direta na conceção e elaboração deste artigo, que participaram na análise e interpretação dos dados, na redação do manuscrito, na revisão das versões e revisão crítica do seu conteúdo e na aprovação da versão final.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

Provenance and Peer Review: Not commissioned; externally peer-reviewed.

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