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Correlation between cardiovascular parameters and glaucomatous changes in the optic nerve in patients with low-output heart failure

Correlação entre parâmetros cardiovasculares e alterações glaucomatosas do nervo óptico em portadores de insuficiência cardíaca congestiva

João Lucas de Oliveira Pegurin Libório[1] https://orcid.org/0000-0002-2770-5284
José Paulo Pinotti Ferreira Junior[1] https://orcid.org/0000-0003-2950-7916
Lucas de Azevedo Melo Uneda[1] https://orcid.org/0000-0002-4739-8867
Guilherme Baptista Rosalem Fraga[1] https://orcid.org/0000-0001-8058-893X
Eduardo Modenesi Felício[1] https://orcid.org/0000-0002-1013-4585
Bruno de Freitas Valbon[2] https://orcid.org/0000-0002-5514-5843

Abstract

Objectives: *To correlate ophthalmoscopic and cardiovascular parameters in patients diagnosed with low-output heart failure (HFrEF) and to evaluate the association between HFrEF and glaucoma-suggestive alterations in the optic nerve.* ***Methods:*** *Descriptive, observational and prospective study, composed of 30 patients diagnosed with HFrEF. The patients were submitted to ophthalmologic examination, which included biomicroscopy, visual acuity, gonioscopy, intraocular pressure (IOP) and central corneal thickness (CCT) measurement. Their cardiovascular parameters evaluation, such as mean arterial pressure (MAP), left ventricular ejection fraction (LVEF), comorbidities and diagnosis time of HFrEF was performed upon a review over their medical chart. The left eye was arbitrarily chosen for statistical analysis of the data. Statistical correlation was performed using the Spearman test, while the comparison was performed using the Mann-Whitney U-test.* ***Results:*** *A high prevalence of peripapillary atrophy (73.3%) was observed, as well as a positive, moderate and statistically significant correlation between LVEF and ocular perfusion pressure (OPP) (r = 0.517; p = 0.004). Despite the lack of significance of the Mann-Whitney U-Test comparisons, a higher prevalence of peripapillary atrophy was found in patients with lower MAP, lower LVEF and lower OPP.* ***Conclusion:*** *HFrEF may be a risk factor for the development of glaucomatous changes in the optic nerve disc. The resulting peripapillary atrophy and low OPP from the contractile deficit may be related to the vascular theory about normal-tension glaucoma development.*

Keywords: *Glaucoma, open anlge; Heart failure; Optic nerve; Intraocular pressure; Optic nerve diseases*

Resumo

Objetivos: Correlacionar parâmetros oftalmoscópicos e cardiovasculares em pacientes com diagnóstico de insuficiência cardíaca com fração de ejeção reduzida (ICFER) e avaliar a associação entre ICFER e alterações do nervo óptico sugestivas de glaucoma. **Métodos:** Estudo descritivo, observacional, prospectivo, composto por amostra 30 pacientes com diagnóstico de ICFER. Os pacientes foram submetidos ao exame oftalmológico, que incluiu biomicroscopia, avaliação da acuidade visual, aferição da PIO (pressão intraocular), gonioscopia e medida de ECC (espessura central corneana). A avaliação de parâmetros cardiovasculares, como PAM (pressão arterial média), FEVE (fração de ejeção do ventrículo esquerdo), comorbidades e tempo de diagnóstico de IC foi realizada a partir de revisão de prontuário médico. Arbitrariamente foi escolhido o olho esquerdo para análise estatística dos dados. A correlação estatística foi realizada através do teste de Spearman, e a comparação através do teste U de Mann-Whitney. **Resultados:** Observou-se uma alta prevalência de atrofia peripapilar (73,3%), além de uma correlação positiva, moderada e estatisticamente significativa entre FEVE e PPO (pressão de perfusão ocular) (r = 0,517; p = 0,004). Apesar da ausência de significância das comparações pelo Teste U de Mann-Whitney, evidenciou-se uma maior prevalência de atrofia peripapilar nos pacientes que apresentavam uma menor PAM, menor FEVE e menor PPO. **Conclusão:** A ICFER pode ser um fator de risco para o desenvolvimento de alterações glaucomatosas no disco do nervo óptico. A atrofia peripapilar e a baixa pressão de perfusão ocular resultantes do déficit contrátil cardíaco podem estar relacionadas com a teoria vascular do desenvolvimento do glaucoma de pressão.

Descritores: Glaucoma de ângulo aberto; Insuficiência cardíaca; Nervo óptico; Pressão intraocular; Doenças do nervo óptico

[1] Academic Course in Medicine, Escola Superior de Ciências, Santa Casa de Misericórdia de Vitória, ES, Brazil.
[2] Department of Ophthalmology, Escola Superior de Ciências, Santa Casa de Misericórdia de Vitória, ES, Brazil.

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Introduction

Glaucoma is a progressive optic neuropathy resulting from specific changes in ganglion cell axons that presents with characteristic structural damage and altered visual field. It affects more than 70 million people globally, being the main cause of irreversible blindness in the world.[1] The disease can remain asymptomatic until more advanced stages. Glaucoma can be divided into two major groups: primary open-angle glaucoma (POAG) and closed-angle glaucoma, the first being the most prevalent (80% of cases). The pathophysiology and factors contributing to the progression of primary open-angle glaucoma are not fully understood. Elevation of intraocular pressure is the main risk factor, and its reduction is the only treatment that currently shows efficacy.[2] However, many patients develop POAG without ocular hypertension, so we should think that other factors may be involved in the development and progression of POAG. One hypothesis is vascular theory. This theory is based on the premise of poor perfusion of the optic nerve leading to apoptosis of the ganglion cells, and consequently a functional visual involvement.[3] Many studies have demonstrated the relation between decreased cardiac function and glaucomatous changes in the optic nerve, which may explain part of the cases of normal pressure POAG1. Even so, the role of congestive heart failure (CHF) in reducing blood flow to the optic nerve head and the development of POAG are still being elucidated, which makes this study a major contribution to the scientific community.

Methods

A prospective, observational and descriptive study carried out at the Department of Ophthalmology of Santa Casa de Misericórdia de Vitória (ES). The sample consisted of 30 patients with heart failure with reduced ejection fraction (HFrEF), with an ejection fraction documented in TTE <55% registered at the Cardiology Ambulatory of the same institution. All participants read and signed the Free and Informed Consent Form.

Patients with diseases of the anterior segment of the eye were excluded.

The patients were submitted to ophthalmologic examination including evaluation of visual acuity, biomicroscopy, intraocular pressure (IOP), gonioscopy, and central corneal thickness (CCT). The visual acuity was evaluated using the Snellen optometric scale. The IOP was carried out by Goldmann's Flattening Tonometry. CCT was obtained by means of an ultrasonic pachymeter. All of the tests above were carried out in patients' both eyes. The evaluation of cardiovascular parameters such as blood pressure (BP), left ventricular ejection fraction (LVEF), comorbidities, and time of diagnosis of HF were carried out based on medical record review. The mean arterial pressure (MAP) was calculated using the following formula: MAP = 1/3 (SBP - DBP) + DBP. Ocular perfusion pressure (OPP) was calculated by the following formula: 2/3 x MAO - IOP.

The left eye was arbitrarily chosen for statistical analysis of the data. Statistical correlation was carried out using the Spearman test, and comparison using the Mann-Whitney U-test.

The research project was approved by the Research Ethics Committee of EMESCAM under number CAAE 78858117.6.0000.5065 (Annex B).

Table 1
Cardiovascular and ophthalmologic parameters

	Mín.	Máx.	Median	Average	Standard deviation	N valid
Age in years	41	91	61	62	12	30
SBP	80	182	120	124	24	30
DBP	40	142	80	82	22	30
Mean blood pressure	53.0	155.3	93.3	96.0	21.7	30
Left Ventricular Ejection Fraction	10.0	64.0	35.0	36.6	12.9	30
Ocular perfusion pressure	23.3	90.5	50.2	51.3	14.7	29
Corneal thickness	496.0	586.0	541.5	539.5	23.6	30
Excavation of the eye	0.1	0.9	0.2	0.3	0.2	30
Time of diagnosis of heart failure (years)	0.5	30.0	8.0	8.3	7.1	27

SBP: systolic blood pressure; DBP: diastolic blood pressure

Results

Prevalence of male (60%) and white (40%) individuals. Of the respondents, 25.8% had a family history of glaucoma, and one patient (3.3%) had a previous diagnosis of this ocular condition. Most of the individuals (93.3%) presented some type of comorbidity along with HFrEF, especially Diabetes Mellitus (50%), Systemic Arterial Hypertension (43.3%), and Atrial Fibrillation (20%). Table 1 summarizes several cardiovascular and ophthalmologic parameters.

In the population analyzed, 78.6% of the people had visual acuity equal to or greater than 20/60 according to Snellen's optometric scale, 80.6% presented Shaffer grade 4 angle to the gonoscopy, and only 2 patients (6.5%) showed loss of the ISNT rule.

No disk hemorrhage at funduscopic examination nor notch of neural rhyme was identified in any of the volunteers evaluated. The integrity of the optic papilla, peripapillary atrophy was found in most of the patients analyzed (73.6%).

There was no statistical significance in the following correlations between ophthalmologic and cardiovascular parameters: CCT x MAP, age x MAP, MAP x IOP, IOP x LVEF, and time of diagnosis of HFrEF x OPP.

When correlating CCT and IOP, a negative, moderate and statistically significant correlation was obtained ($r = -0.435$ and $p = 0.018$), that is, patients with greater corneal thickness had lower intraocular pressures.

The scatter plot (Figure 1) shows that there was a positive, moderate, and statistically significant correlation between left ventricular ejection fraction and ocular perfusion pressure. Patients with greater cardiac contractile dysfunction had lower ocular perfusion pressure.

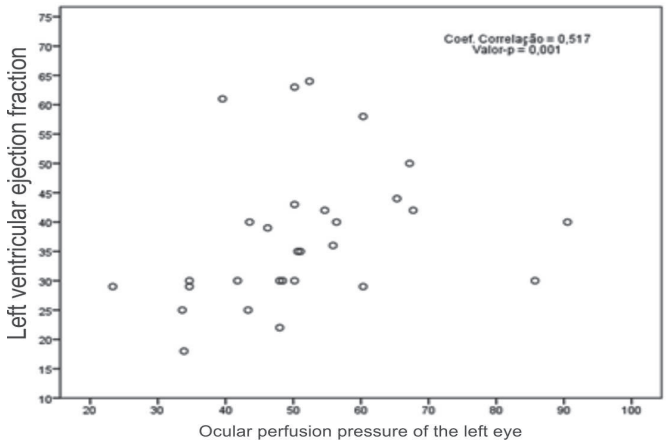

Figure 1: Correlation between LVEF and OPP

Figure 2 shows the presence or absence of peripapillary atrophy in the left eye with four variables: mean arterial pressure, left ventricular ejection fraction, time of diagnosis of HFrEF (in years), and ocular perfusion pressure of the left eye. Despite the lack of significance of the Mann-Whitney U-Test comparisons, it was observed that the average MAP was lower in patients who presented peripapillary atrophy (94.12 mmHg ± 21.93) than the average of patients who did not present atrophy (101.39mmHg ± 23.23). The average left ventricular ejection fraction was also lower in patients with peripapillary atrophy (35.95% ± 13.49) when compared to the group without atrophy (38.00% ± 12.77). The average time of diagnosis of HFrEF was higher in patients without peripapillary atrophy (11.0 years ± 10.2) than in patients with atrophy (7.3 years ± 5.7). It was also evidenced that the average ocular perfusion pressure was lower in patients with peripapillary atrophy (49.76 mmHg ± 14.82) when compared to the group without atrophy (55.45 mmHg ± 15.60).

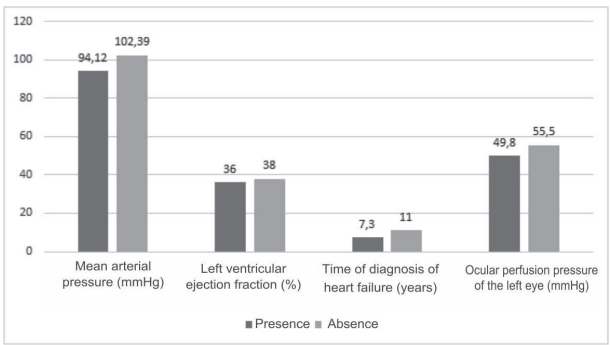

Figure 2: Comparison between hemodynamic parameters and presence or absence of peripapillary atrophy

Discussion

Comparing the present study to the epidemiology of glaucoma, we found some differences. In a population-based screening study for glaucoma in the city of São Paulo, 66% of the patients were female, with a majority of black people(4), whereas in our analysis male (60%) white (40%) subjects prevailed. We must consider that our sample was formed by patients with HFrEF, which probably justifies the different prevalences.

Patients with glaucoma have significantly more comorbidities than the general population. Studies have shown that more than half (50.5%) of patients with glaucoma also had systemic arterial hypertension, and 30.2% had diabetes mellitus.[5] HFrEF patients also have multiple comorbidities. The prevalence of diabetes mellitus in this population is very similar to that obtained in patients with glaucoma (30%).[6] Systemic arterial hypertension, however, is a more frequent comorbidity in patients with HFrEF than in patients diagnosed with glaucoma, and is present in 66% of patients with reduced cardiac ejection fraction.[7]

According to a previous Brazilian study also correlating heart failure with glaucoma, the average age of the patients evaluated at the time was 54.8 years, whereas in the present study it was 62 years. Regarding blood pressure, the average systolic blood pressure obtained at the time was 110.4 mmHg, and the diastolic blood pressure was 75.2 mmHg, whereas in the current study the average SBP was 124 mmHg and DBP was 82 mmHg. Regarding the average MAP and ocular perfusion pressure, the values obtained by the Brazilian researchers in the previous study were 86.9 mmHg and 45.6 mmHg, whereas in the present study the values found were 96 and 51.3 mmHg, respectively. The average value of LVEF was the same as that obtained in the two studies (35%).[1]

The differences in MAP and ocular perfusion pressure are probably due to the different stages of heart failure among the patients analyzed and the difference in the intensity of the treatment of HFrEF, resulting in a greater pressure reduction in the previous Brazilian study than in the patients analyzed in the present study.

In our study, 90.3% of patients presented Shaffer's gonioscopy grades 3 or 4, representing a wide open angle with no risk of closure.[8] Currently, it is known that patients with normal pressure glaucoma, as a rule, do not present changes to the gonioscopy,[9] which is in agreement with what we obtained in our sample.

As for the ISNT rule, only 2 patients (6.5%) had their standard changed. Currently, the real role of breaking the ISNT rule in the early diagnosis of glaucoma is questioned. A study in India used the measures of the ISNT rule to assess whether early changes in its parameters could indicate glaucomatous conditions in the optic nerve. It was concluded breaking the ISNT rule is practically imperceptible in early-stage glaucomas, and according to this study it is not a good method for screening the disease.[10]

The absence of disk hemorrhage and the presence of notch in 6.6% of patients were similar results to those found in a similar study carried out in Brazil, which also did not show disk hemorrhage and identified notch in 10.7% of patients with HFrEF analyzed1. For comparison, studies indicate that the prevalence of notch in the general population older than 49 years is 5.7%.[11] Interestingly, this same study demonstrated that the presence of notch was more frequent in patients who had peripapillary atrophy.[11] The relation between HFrEF and peripapillary atrophy is not known yet, but ischemic changes of the microcirculation due to the decrease in the ejection fraction observed in heart failure may justify the high prevalence of peripapillary atrophy in this group of patients, and consequently the development of neural rhyme notch in cardiac patients.

Regarding the correlation between CCT and MAP, no statistical significance was obtained (r= 0.102; p = 0.599). A recent study showed that said variables do not really correlate significantly,[12] corroborating the findings of the present study.

When correlating MAP with IOP, a negligible correlation was obtained (r = 0.102), with no statistical significance (p = 0.599). The sample size probably interfered with the significance of the data obtained, since it has been demonstrated that MAP has a positive and statistically significant correlation with IOP.[13]

In the present study, the correlation between LVEF and IOP had a correlation coefficient without statistical significance (r = -0.094; p = 0.627). No other studies investigating such correlation were found.

When correlating CCT with IOP, a negative, moderate and statistically significant correlation was observed (r = -0.435 and p = 0.018). Said result was surprising since it goes against what is known about the aforementioned relation. Classically, there is a linear relation between IOP and CCT, i.e., the higher the CCT the higher the IOP.[14] One hypothesis for the divergence observed would be the small sample size of the present study along with the fact that it comprises mainly elderly people (average of 62 years). It has already been shown that advancing age alters the viscoelastic properties of the cornea, which may decrease the accuracy of IOP measurement in the elderly.[15]

In the sample analyzed, a positive, moderate and statistically significant correlation was obtained between LVEF and OPP (r = 0.517; p = 0.004). That is, patients with greater left ventricular contractile dysfunction had lower ocular perfusion pressure. A Brazilian study has already shown that the average ocular perfusion pressure of individuals with HFrEF is 16.2% lower than that of individuals without heart disease.[1] Such changes are expected since cardiac dysfunction associated with multiple hypotensive and chronotropic negative drugs such as beta-blockers, ACE inhibitors and diuretics leads to a decrease in mean arterial pressure, and consequently to ocular perfusion pressure. A national study formulated a hypothesis for such ocular perfusional deficit of cardiac patients. It was demonstrated that patients with chronic heart failure have higher ophthalmic artery resistive index than individuals without heart disease, probably due to a higher sympathetic tone in response to ventricular dysfunction, culminating with arterial vasoconstriction and decreased ocular perfusion.[16]

In the sample analyzed in the study, no statistically significant correlation was found between the time of diagnosis of heart failure and OPP (r = 0.168; p = 0.401). No other studies showing such a comparison were found.

The current study also related the presence or absence of peripapillary atrophy with four variables: mean arterial pressure, left ventricular ejection fraction, time of diagnosis of HFrEF (in years), and ocular perfusion pressure. Despite the lack of significance of the Mann-Whitney U-Test comparisons, the result elicited hypotheses regarding the actual hemodynamic influence on the genesis of peripapillary atrophy.

The association between peripapillary atrophy and glaucoma is not unanimous. Experimental studies in monkeys have demonstrated no increase in atrophy after elevation of the intraocular pressure, and the presence of said atrophy was also not associated with the development of glaucomatous changes in neuroretinal rhyme.[17] In contrast, prospective longitudinal studies in humans have demonstrated that there is a statistically significant correlation between peripapillary atrophy and changes in the neuroretinal ring, leading to progressive loss of visual field.[18] Such data suggest that the presence of peripapillary atrophy in humans may precede the onset of glaucoma. In our study, despite the statistical insignificance, it was observed that individuals with lower left ventricular ejection fraction and lower MAP tend to have more peripapillary atrophy, which in the long term may culminate in the development of glaucoma even with normal IOP. The pathophysiology of normal pressure glaucoma in these cases remains unknown, with the main hypothesis being the deficient blood supply in the optic nerve region.[3] Based on this thesis of abnormal blood flow, patients with HFrEF present an important risk factor for the development of normal pressure glaucoma, since they are known to be hypotensive due to the established therapy, and with a decrease in ventricular function due to base heart disease. Lower LVEF and MAP may lead to a perfusional optic nerve deficit, altering its microstructure and gradually affecting the visual field, culminating with normal intraocular pressure glaucoma. The use of new technologies for peripapillary capillary microcirculation analysis such as Angio-OCT, which allows the evaluation and measurement of intraocular artery morphology as well as its blood flow, can help in the early diagnosis of such perfusion changes,[19] avoiding future visual complications resulting from a late diagnosis.

Referências

1. Meira-Freitas D, Melo LA Jr, Almeida-Freitas DB, Paranhos A Jr. Glaucomatous optic nerve head alterations in patients with chronic heart failure. Clin Ophthalmol. 2012;6:623–9.
2. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014;311(18):1901–11.
3. Fan N, Wang P, Tang L, Liu X. Ocular Blood Flow and Normal Tension Glaucoma. BioMed Res Int. 2015;2015:308505.
4. Póvoa CA, Nicolela MT, Valle AL, Gomes LES, Neustein I. Prevalência de glaucoma identificada em campanha de detecção em S?o Paulo. Arq Bras Oftalmol. 2001;64(4):303–7.
5. Lin HC, Chien CW, Hu CC, Ho JD. Comparison of comorbid conditions between open-angle glaucoma patients and a control cohort: a case-control study. Ophthalmology. 2010;117(11):2088–95.
6. van Deursen VM, Urso R, Laroche C, Damman K, Dahlström U, Tavazzi L, et al. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. Eur J Heart Fail. 2014;16(1):103–11.
7. Dunlay SM, Weston SA, Jacobsen SJ, Roger VL. Risk factors for heart failure: a population-based case-control study. Am J Med. 2009;122(11):1023–8.
8. Almeida HG, Suzuki Junior ER, Sakata LM, Torres RJ. Gonioscopia: proposta de classificação (APIC). Rev Bras Oftalmol. 2010;69(5):332–41.
9. Tavares IM, Mello PA. Glaucoma de pressão normal. Arq Bras Oftalmol. 2005 Jul;68(4):565–75.
10. Sihota R, Srinivasan G, Dada T, Gupta V, Ghate D, Sharma A. Is the ISNT rule violated in early primary open-angle glaucoma—a scanning laser tomography study. Eye (Lond). 2008;22(6):819–24.
11. Healey PR, Mitchell P. Presence of an optic disc notch and glaucoma. J Glaucoma. 2015;24(4):262–6.
12. Schuster AK, Fischer JE, Vossmerbaeumer U. Central corneal thickness in spectral-domain OCT and associations with ocular and systemic parameters. J Ophthalmol. 2016;2016:2596956.
13. Sirvi GC, Kaumar J. Study of relationship between intraocular pressure, pulse pressure and mean arterial pressure in different age groups in Western Rajasthan. Int J Appl Res. 2016;2(3):279–82.
14. Sakata K, Figueira AL, Guimarães AC, Schmitt AJ, Scapucin L, Barros LG, et al. Estudo da correlaçãoo entre pressão intra-ocular e espessura corneana central (projeto glaucoma). Arq Bras Oftalmol. 2000;63(5):355-8.

15. Valbon BF, Ambrósio R Jr, Fontes BM, Alves MR. Effects of age on corneal deformation by non-contact tonometry integrated with an ultra-high-speed (UHS) Scheimpflug camera. Arq Bras Oftalmol. 2013;76(4):229–32.
16. Almeida-Freitas DB, Meira-Freitas D, Melo LA Jr, Paranhos A Jr, Iared W, Ajzen S. Color Doppler imaging of the ophthalmic artery in patients with chronic heart failure. Arq Bras Oftalmol. 2011;74(5):326–9.
17. Derick RJ, Pasquale LR, Pease ME, Quigley HA. A clinical study of peripapillary crescents of the optic disc in chronic experimental glaucoma in monkey eyes. Arch Ophthalmol. 1994;112(6):846–50.
18. Uchida H, Ugurlu S, Caprioli J. Increasing peripapillary atrophy is associated with progressive glaucoma. Ophthalmology. 1998;105(8):1541–5.
19. Igarashi R, Ochiai S, Sakaue Y, Suetake A, Iikawa R, Togano T, et al. Optical coherence tomography angiography of the peripapillary capillaries in primary open-angle and normal-tension glaucoma. PLoS One. 2017;12(9):e0184301.

Autor correspondente:
João Lucas de Oliveira Pegurin Libório
E-mail: joaolucasopl@gmail.com