

## SHOULD WE SCREEN FOR ASYMPTOMATIC LEFT VENTRICULAR DYSFUNCTION IN GLAUCOMA PATIENTS?

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**Background:** The aim of the study was to assess the frequency of asymptomatic left ventricular dysfunction in primary open-angle glaucoma patients.

**Patients and Methods:** Two-dimensional and pulsed Doppler echocardiography of transmitral flow was performed on 31 glaucoma patients and 27 controls.

**Results:** No significant difference was found in early (E) and late (A) transmitral filling velocity, velocity time integral E wave (VTIE) and A wave (VTIA), left ventricular end-diastolic pressure, pulmonary capillary wedge pressure, left ventricular ejection fraction (EF) and fractional shortening (FS). A significant difference was found in ratio E/A ( $P=0.04$ ) and ratio VTIA/VTIE ( $P=0.05$ ), although all obtained values were within the 95% confidence limit for the corresponding age.

**Conclusion:** Our study tends to indicate the possibility of dysfunction of myocardial relaxation in glaucoma patients, which might be partially attributed to systemic vascular dysregulation.

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**Key Words:** Open-angle glaucoma, Doppler echocardiography, diastolic dysfunction.

The pathogenesis of glaucoma remains unclear. In addition to rheological factors, indirect evidence suggests that vascular factors may be involved, probably by reducing the blood supply to the optic nerve.<sup>1-5</sup> Microcirculatory impairment of the anterior optic nerve has been invoked as a potential causative factor or contributor to glaucomatous optic neuropathy.<sup>6</sup> Glaucoma, especially normal-tension glaucoma, is significantly associated with the occurrence of episodic asymptomatic myocardial ischemia, with an increased incidence of cardiovascular disease and risk factors.<sup>7,8</sup>

Cardiovascular abnormalities as well as myocardial ischemia are more often observed in glaucoma patients than in normals.<sup>9,10</sup> Some of these patients may go through a phase of asymptomatic left ventricular dysfunction (ALVD), where objective measurements reveal impaired cardiac contractility, but overt heart failure is not present.<sup>11</sup> The purpose of this study was to determine the frequency of ALVD in glaucoma patients. ALVD is estimated to be present in 1%-2% of the population.<sup>12</sup>

### Patients and Methods

The study included 31 patients with primary (high tension) open-angle glaucoma (12 males and 19 females),

aged  $58.5 \pm 6.5$  years and 27 healthy volunteers (14 males and 13 females), aged  $56.9 \pm 7.4$  years. Diagnostic criteria for primary open-angle glaucoma were intraocular pressure (IOP) greater than 21 mm Hg on a diurnal curve and without treatment, open anterior chamber angle, no evidence of underlying ocular or systemic cause of high IOP, glaucomatous cupping of the optic disc and glaucomatous visual field defects.

All patients were examined using two-dimensional echocardiography studies and pulsed Doppler echocardiography with a 3.5 MHz transducer (Diasonics DRF 4000, USA). Patients with valvular and pericardial heart disease, left ventricular hypertrophy and systemic hypertension were excluded. Latent coronary artery disease was excluded after normal upright exercise testing. Myocardial function was expressed in terms of left ventricular developed pressure and ejection fraction. The cardiac cycle consisted of the contraction and ejection phase of systole and the relaxation and filling phase of diastole. Left ventricular (LV) systolic contraction and ejection were evaluated using the LV ejection fraction (EF) and fractional shortening (FS). LV diastolic filling parameters tested were fast inflow (E wave) and late inflow (A wave), pressure at the end of filling (LVEDP), as well as a pulmonary capillary wedge pressure (PCWP), and their relationship.

From the parasternal short-axis derived M-modes of the left ventricle, the end-diastolic and end-systolic dimensions were measured. Left ventricular ejection fraction and fractional shortening were obtained according to the Kessler.<sup>13</sup> Left ventricular diastolic function was evaluated by the pulsed Doppler technique measuring mitral venous flow.<sup>14,15</sup> The following transmitral Doppler parameters

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TABLE 1. The results of echographic and Doppler examinations.

	Glaucoma subjects (n=31)	Control subjects (n=27)	P-value (Mann-Whitney U-test)	
EF (%)	66.8±9.6	66.9±8.1	0.99	z=0.007
FS (%)	32.4±6.6	32.3±6.2	0.97	z=0.03
E (cms <sup>-1</sup> )	55.3±9.4	59.4±13.4	0.45	z=0.75
A (cms <sup>-1</sup> )	59.4±10.4	54.7±10.4	0.09	z=1.68
E/A	0.96±0.23	1.11±0.28	0.04	z=2.04
VTIE (cm)	7.2±1.8	7.3±1.5	0.95	z=0.06
VTIA (cm)	5.2±1.4	4.4±1.5	0.07	z=1.81
VTIA/VTIE	0.92±0.9	0.63±0.24	0.05	z=1.97
LVEDP (mmHg)	12.3±4.6	9.92±4.3	0.08	z=1.69
PCWP (mmHg)	12.0±4.8	10.6±4.1	0.09	z=1.70

EF=ejection fraction; FS=fractional shortening; E=peak velocity of early mitral flow; A=peak velocity of late mitral flow; VTIE=velocity time integral of the E wave; VTIA=velocity time integral of the A wave; LVEDP=left ventricular end-diastolic pressure; PCWP=pulmonary capillary wedge pressure. Values expressed as mean±SD.

were analyzed: mitral flow parameters, including peak early (E) and late (A) transmitral filling velocities, their ratio (E/A), velocity time integral E wave (VTIE) and A wave (VTIA) and their ratio (VTIA/VTIE).<sup>14-16</sup> Left ventricular end-diastolic pressure and pulmonary capillary wedge pressure were calculated according to the formulas of Stork et al.<sup>16</sup>

All results were expressed as mean ± standard deviation. Comparisons between the groups used the Mann-Whitney rank sum test. The chi-square test and Student's t-test were used to compare patient's data such as age and sex. P-values <0.05 were considered to be significant.

## Results

The results of echographic and Doppler examinations are given in Table 1. Using the Student's t-test and chi-square test for independence, we did not find a significant difference between the two groups in age ( $P=0.39$ ) and sex ( $P=0.29$ ). Systolic function assessed by EF and FS was not different between glaucoma patients and controls ( $P=0.99$ ;  $P=0.97$ ). A significant difference was found concerning mitral flow parameters: ratio E/A ( $P=0.04$ ) and ratio VTIA/VTIE ( $P=0.05$ ). No significant difference was found between groups concerning early and late transmitral filling velocities ( $P=0.45$ ;  $P=0.09$ ), VTIE ( $P=0.95$ ), VTIA ( $P=0.07$ ), LVEDP ( $P=0.08$ ) and PCWP ( $P=0.09$ ) between the groups.

## Discussion

Cardiovascular disease may play an important role in the development and progression of glaucomatous optic neuropathy independent of intraocular pressure, which may be an indirect index of cardiovascular disorders.<sup>17</sup> A large number of studies have shown that glaucomatous optic neuropathy is associated with systemic cardiovascular disease, especially in the elderly.<sup>2,5,7-9,18,19</sup> The higher prevalence of cardiovascular disease, particularly of an ischemic nature, in elderly glaucoma patients was suggestive of a generalized systemic vascular

abnormality.<sup>18,19</sup> Ischemic heart disease was found to be more prevalent among patients with senile sclerotic glaucoma.<sup>17</sup> Asymptomatic myocardial ischemia was found in normal tension and open-angle glaucoma in middle-aged patients.<sup>7</sup>

Diastolic function of the left ventricle plays a major role in producing the signs and symptoms of heart failure in diseases of the myocardium. Among mitral flow parameters used to evaluate left ventricular diastolic filling, a significant difference was found between E/A ratio and VTIA/VTIE ratio, although these findings were within the 95% confidence limit for the corresponding age.<sup>20-22</sup> It is quite possible that these differences in the Doppler waveforms tend to indicate the possibility of dysfunction of myocardial relaxation in glaucoma subjects.

At the time of Doppler echocardiographic examination, the glaucoma patients were without treatment, which probably could have an influence on the parameters tested. Some evidence suggests that vascular endothelial dysfunction could contribute to vascular deficit in glaucoma.<sup>23-25</sup> An abnormal vascular endothelial function has been shown to occur in heart failure, and consequently our findings could, theoretically, be explained as a part of systemic vascular dysregulation.<sup>26</sup>

There are several limitations of this study which should be noted. First, it becomes more difficult to determine the presence of abnormalities of diastolic filling from the mitral flow velocity curves in patients with normal left ventricular function. Second, the values of echographic parameters in our glaucoma patients were within the normal range for the age of the group. Finally, this study was conducted using a relatively small number of patients; our results should be confirmed by larger studies.

## References

1. Flammer J. The vascular concept of glaucoma. *Surv Ophthalmol* 1994;38 (Suppl):S3-S6.
2. Flammer J. To what extent are vascular factors involved in the pathogenesis of glaucoma. In: Kaiser HJ, Flammer J, Hendrickson PH, editors. *Ocular blood flow*. London: Karger, 1996:12-39.
3. Hoyng PF, de Jong N, Oosting H, Stilma J. Platelet aggregation, disc hemorrhage and progressive loss of visual fields in glaucoma. A seven years follow up study on glaucoma. *Int Ophthalmol* 1992;16:65-73.
4. Bojic L, Škare-Librenjak LJ. Circulating platelet aggregates in glaucoma. *Int Ophthalmol* 1999;22:151-4.
5. Gasser P. Why study vascular factors in glaucoma? *Int Ophthalmol* 1999;22:221-5.
6. Flammer J, Orgul S. Optic nerve blood-flow abnormalities in glaucoma. *Prog Retin Eye Res* 1998;17:267-89.
7. Waldmann E, Gasser P, Dubler B, Huber C, Flammer J. Silent myocardial ischemia in glaucoma and cataract patients. *Graefes Arch Clin Exp Ophthalmol* 1996;234:595-8.
8. Mermoud A. Glaucoma and risk factors. Comparative study of cardiovascular risk factors in primary open angle glaucoma, normal pressure glaucoma and simple ocular hypertension. *Rev Med Suisse Romande* 1996;116:51-8.
9. Perasalo R, Perasalo J, Raita CH. Electrocardiographic changes in institutionalized geriatric glaucoma patients. *Graefes Arch Clin Exp Ophthalmol* 1992;230:213-9.
10. Kaiser HJ, Flammer J, Burckhardt D. Silent myocardial ischemia in glaucoma patients. *Ophthalmologica* 1993;207:6-7

11. McMurray JV, McDonagh TA, Davie AP, Cleland JGF, Francis CM, Morisson C. Should we screen for asymptomatic left ventricular dysfunction to prevent heart failure? *Eur Heart J* 1998;19:842-6.
12. McDonagh TA, Morisson CE, Lawrence A, Tunstall-Pedoe H, Ford I, McMurray JU, Dargie HJ. Symptomatic and asymptomatic left ventricular systolic dysfunction in an urban population. *Lancet* 1997;350:829-33.
13. Kessler KM. Ejection fraction derived by M-mode echocardiography: a table and comments. *Cathet Cardiovasc Diagn* 1979;5:295-9.
14. Poulsen SH, Jensen SE, Gotzsche O, Egstrup K. Evaluation and prognostic significance of left ventricular diastolic function assessed by Doppler echocardiography in the early phase of a first acute myocardial infarction. *Eur Heart J* 1997;18:1882-9.
15. Paillole C, Dahan M, Paycha F, Solal AC, Passa P, Gourgon R. Prevalence and significance of left ventricular filling abnormalities determined by Doppler echocardiography in young type I (insulin-dependent) diabetic patients. *Am J Cardiol* 1989;64:1010-6.
16. Stork TV, Muller RM, Piske JG, Ewert CO, Hochrein H. Noninvasive measurement of left ventricular filling pressures by means of transmitral pulsed Doppler ultrasound. *Am J Cardiol* 1989;64:655-60.
17. Hayreh SS. The role of age and cardiovascular disease in glaucomatous optic neuropathy. *Surv Ophthalmol* 1999;43(Suppl):S27-S42.
18. Broadway DC, Drance SM. Glaucoma and vasospasm. *Br J Ophthalmol* 1998;82:862-70.
19. Nicoleta MT, Drance SM. Various glaucomatous optic nerve appearances: clinical correlations. *Ophthalmol* 1996;103:640-9.
20. Maron BJ, Spirito P, Green KJ, Wesley YE, Bonow RO, Arce J. Noninvasive assessment of left ventricular diastolic function by pulsed Doppler echocardiography in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1987;10:733-42.
21. Cohen GI, Pietrolungo JF, Thomas JD, Klein AL. A practical guide to assessment of ventricular diastolic function using Doppler echocardiography. *J Am Coll Cardiol* 1996;27:1753-60.
22. Working Group Report. How to diagnose diastolic heart failure. *Eur Heart J* 1998;19:990-1003.
23. Cellini M, Possati GL, Profazio V, Sbrocca M, Caramazza N. Color Doppler imaging and plasma levels of endothelin-1 in low tension glaucoma. *Acta Ophthalmol Scand* 1997;75 (Suppl 224):11-3.
24. Cellini M, Caramazza R. Chronic open angle glaucoma and low tension glaucoma: endothelin-1 levels in plasma and aqueous humor. *Acta Ophthalmol Scand* 1999;77 (Suppl 229):7-8.
25. Haefliger IO, Dettmann E, Liu R, Meyer P, Prunte C, Meserli J, Flammer J. Potential role of nitric oxide and endothelin in the pathogenesis of glaucoma. *Surv Ophthalmol* 1999;43(Suppl):S51-S8.
26. Ferrari R, Bachetti T, Agnolletti L, Comini L, Curello S. Endothelial function and dysfunction in heart failure. *Eur Heart J* 1998;19(Suppl):41-7.