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## Original article

# Morphological and morphometric changes in rat optic nerve microvessels in a glaucoma experimental model<sup>☆</sup>



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## ABSTRACT

**Aim:** To study the morphological and morphometric changes produced in the capillaries of the optic nerve (ON) head and initial portion after the experimental increase in intraocular pressure (IOP).

**Material and methods:** Wistar rats underwent cauterization of three episcleral veins, which produced an immediate increase in the IOP, and was maintained for 3 months. Sagittal sections of the eyeball were studied with immunohistochemical techniques, using a primary antibody to GLUT-1. The GLUT-1 positive capillaries were counted, and measurements were made of the area, perimeter and mean diameter.

**Results:** Microscopic examination of sections of the ON of control rats revealed a lower density and larger caliber of capillaries in the prelaminar region as compared with the other regions of the OP ( $p < .05$ ). Comparison between the control and the experimental groups showed a reduction in capillary density (except in the prelaminar region) and a smaller size in all the areas of the OP studied, but less evident in the initial portion ( $p < .05$ ).

**Conclusions:** The increase in IOP was associated with significant qualitative and quantitative changes in the capillaries of the laminar and poslaminar regions of the OP head. These changes appear to return toward parameters compatible with normality in the initial portion of the OP, an area where the vascular collapse was less evident. These findings might explain the significant reduction in ocular blood flow seen in patients with primary open-angle glaucoma.

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## Cambios morfológicos y morfométricos en los capilares del nervio óptico de rata en un modelo experimental de glaucoma

### R E S U M E N

#### Palabras clave:

Nervio óptico  
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GLUT-1  
Barrera hematoencefálica

**Objetivo:** Estudiar los cambios morfológicos y morfométricos producidos en los capilares de la cabeza del nervio óptico (NO) y de su porción inicial, después de la elevación experimental de la presión intraocular (PIO).

**Material y métodos:** Se utilizaron ratas Wistar que fueron sometidas a cauterización de 3 venas episclerales, con el resultado inmediato de elevación de la PIO, manteniéndose esta durante 3 meses. Se realizaron secciones sagitales del globo ocular y se aplicaron técnicas inmunohistoquímicas, mediante un anticuerpo para GLUT-1. Se procedió al recuento de los capilares GLUT-1 positivo y se midieron área, perímetro y diámetro medio.

**Resultados:** El examen microscópico de las secciones del NO de las ratas controles demostró una menor densidad de capilares y un mayor caliber de los mismos en la región prelaminar, respecto a las demás regiones del NO ( $p < 0,05$ ). Cuando se compararon los grupos control y experimental se observó una disminución en la densidad de capilares (excepto en la región prelaminar) y un menor tamaño de los mismos en todas las zonas del NO analizadas, menos evidente en la porción inicial ( $p < 0,05$ ).

**Conclusiones:** El aumento de la PIO se relaciona con cambios cualitativos y cuantitativos de los capilares de las regiones laminar y poslaminar de la cabeza del NO, y parecen recuperarse hacia parámetros compatibles con la normalidad en la porción inicial del NO, donde el colapso vascular es menos evidente. Estos hallazgos podrían explicar la reducción significativa del flujo sanguíneo ocular observada en pacientes con glaucoma primario de ángulo abierto.

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## Introduction

The topographic region corresponding to the optic nerve head (ONH) is an anatomical crossroads with very peculiar characteristics, making it vulnerable to numerous neuropathies, notably glaucoma. A number of risk factors are considered in said disease, mainly increased intraocular pressure (IOP). In addition, several clinical-epidemiological and experimental studies have demonstrated that vascular insufficiency arises at the ONH in the course of glaucomatous disease which leads to diminished blood supply for its structural components.<sup>1,2</sup>

ONH vascularization is complex and is mainly derived from the posterior ciliary arteries and the central retinal artery.<sup>3,4</sup> Alterations in the posterior ciliary circulation in the ONH have been identified as one of the courses of glaucoma<sup>5</sup> as well as common ischemic diseases.<sup>6</sup>

ONH capillaries are characterized by: (1) the presence of occlusive unions between endothelial cells which prevent the exchange of substances between blood and the interstitial space; (2) shortage of pinocytosis vesicles which provide limited trans-endothelial transport of a large range of substrates; and (3) the existence of specific membrane transport proteins involved in regulating the passage of molecules through capillary walls. However, even though the capillaries of the optic nerve (ON) prelaminar region (PLR) exhibit a morphology similar to the capillaries of other regions of

this nerve structure, they feature intense transendothelial permeability regulated by the presence of abundant pinocytosis vesicles.<sup>7</sup>

A range of transport molecules have been utilized for studying the characteristics of the blood-brain barrier, including the glucose transporter family (GLUT)<sup>8</sup> which enables glucose, the main energy substrate of the brain, to enter the cell. Specifically, isoform GLUT-1 has been utilized as a marker for the hemato-ocular barrier<sup>7</sup> due to its presence in the membrane of endothelial cells and on the astrocyte "feet" surrounding the capillary.

Previous studies carried out by our group utilizing an experimental ocular hypertension rat model similar to that developed by Shareef et al.,<sup>9</sup> has evidenced that chronic high IOP induces an obstruction in the anterograd axonic transport<sup>10</sup> and an increase in the expression of nitric oxide synthase 1 and 2,<sup>11</sup> compatible with the death of retina ganglion cells, one of the characteristics of glaucomatous optic neuropathy.

Due to the importance of microvascularization for the ONH and the role it plays in glaucomatous disease, in this study we have analyzed whether experimental chronic IOP increase gives rise to significant changes in the ON head. In this regard, we have used the GLUT-1 isoform of the glucose carrier to immunohistochemically mark the capillaries of the various ON regions: PLR, laminar region (LR) and post-laminar region (PR) of the ONH, as well as its initial portion, evaluating the size and density of said capillaries.

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