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ABOUT COVER

Peer Reviewer of *World Journal of Cardiology*, Atarodsadat Mostafavinia, PhD, Assistant Professor, Department of Anatomical Sciences, Faculty of Medicine, Tehran Medical sciences, Azad University, Tehran, Iran.
a.mostafavinia@gmail.com

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Unveiling the silent link: Normal-tension glaucoma's enigmatic bond with cardiac blood flow

Prasanna Venkatesh Ramesh, Arvind Kumar Morya, Ajanya K Aradhya, Pavithra Pannerselvam, Sai Thaejesvi Gopalakrishnan, Shruthy Vaishali Ramesh, Aji Kunnath Devadas, Navaneeth Krishna

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Prasanna Venkatesh Ramesh, Department of Glaucoma and Research, Mahathma Eye Hospital Private Limited, Trichy 620017, Tamil Nadu, India

Arvind Kumar Morya, Department of Ophthalmology, All India Institute of Medical Sciences, Hyderabad 508126, Telangana, India

Ajanya K Aradhya, Aji Kunnath Devadas, Navaneeth Krishna, Department of Optometry and Visual Science, Mahathma Eye Hospital Private Limited, Trichy 620017, Tamil Nadu, India

Pavithra Pannerselvam, Sai Thaejesvi Gopalakrishnan, Mahathma Eye Hospital Private Limited, Trichy 620017, Tamil Nadu, India

Shruthy Vaishali Ramesh, Department of Cataract and Refractive Surgery, Mahathma Eye Hospital Private Limited, Trichy 620017, Tamil Nadu, India

Corresponding author: Prasanna Venkatesh Ramesh, MBBS, MS, DNB, Department of Glaucoma and Research, Mahathma Eye Hospital Private Limited, No. 6 Seshapuram, Tennur, Trichy - 620017, Tamil Nadu, India. email2prajann@gmail.com

Abstract

This comprehensive review embarks on a captivating journey into the complex relationship between cardiology and normal-tension glaucoma (NTG), a condition that continues to baffle clinicians and researchers alike. NTG, characterized by optic nerve damage and visual field loss despite normal intraocular pressure, has long puzzled clinicians. One emerging perspective suggests that alterations in ocular blood flow, particularly within the optic nerve head, may play a pivotal role in its pathogenesis. While NTG shares commonalities with its high-tension counterpart, its unique pathogenesis and potential ties to cardiovascular health make it a fascinating subject of exploration. It navigates through the complex web of vascular dysregulation, blood pressure and perfusion pressure, neurovascular coupling, and oxidative stress, seeking to uncover the hidden threads that tie the heart and eyes together in NTG. This review explores into the intricate mechanisms connecting cardiovascular factors to NTG, shedding light on how cardiac dynamics can influence ocular health, particularly in cases where intraocular pressure remains within the normal range. NTG's enigmatic nature, often characterized by seemingly contradictory risk factors and clinical profiles, underscores the need for a holistic approach to patient care. Drawing parallels to cardiac health, we examine into the shared vascular terrain connecting the heart and the

eyes. Cardiovascular factors, including systemic blood flow, endothelial dysfunction, and microcirculatory anomalies, may exert a profound influence on ocular perfusion, impacting the delicate balance within the optic nerve head. By elucidating the subtle clues and potential associations between cardiology and NTG, this review invites clinicians to consider a broader perspective in their evaluation and management of this elusive condition. As the understanding of these connections evolves, so too may the prospects for early diagnosis and tailored interventions, ultimately enhancing the quality of life for those living with NTG.

Key Words: Normal tension glaucoma; Vascular dysregulation; Ocular blood flow; Blood pressure; Perfusion pressure; Oxidative stress

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Core Tip: Cardiovascular disease and glaucoma may appear unrelated at first glance, but recent research suggests a potential link between the two seemingly distinct health issues. This review delves into the complex interplay of vascular dysregulation, blood pressure, perfusion pressure, neurovascular coupling, and oxidative stress. Furthermore, certain medications frequently prescribed for managing cardiovascular disease and high blood pressure, such as beta-blockers, may influence blood flow to the eyes. This, in turn, could potentially increase the risk of glaucoma in some individuals. This research highlights how cardiac dynamics can impact ocular health, even when intraocular pressure remains within the normal range.

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INTRODUCTION

Cardiovascular disease and glaucoma may appear unrelated at first glance, but recent research suggests a potential link between the two seemingly distinct health issues. Glaucoma is a progressive optic neuropathy with an unknown origin. There's a hypothesis suggesting that vascular factors play a role in glaucoma's pathophysiology. This review delves into the complex interplay of vascular dysregulation, blood pressure, perfusion pressure, neurovascular coupling, and oxidative stress. These factors may have significant roles in connecting the cardiovascular system with the eyes, especially in normal-tension glaucoma (NTG). Furthermore, certain medications frequently prescribed for managing cardiovascular disease and high blood pressure, such as beta-blockers, may influence blood flow to the eyes. This, in turn, could potentially increase the risk of glaucoma in some individuals. This research highlights how cardiac dynamics can impact ocular health, even when intraocular pressure remains within the normal range.

THE VASCULAR WEB OF NTG

Exploring the intricacies of normal tension glaucoma, we delve into the 'Vascular Web' that underlies this condition, where ocular blood flow, perfusion pressure, and autonomic control come together. In the complex vascular system of NTG, a study revealed asymmetric visual field damage despite stable intraocular pressure. Using color Doppler imaging, the study confirmed that retrobulbar vascular dysregulation significantly contributes to glaucoma progression, particularly in normal tension glaucoma patients with progressive visual field damage. Vascular dysregulation, the inadequate regulation of blood flow for tissue needs, includes primary vascular dysregulation (PVD, formerly called vasospastic syndrome) and secondary vascular dysregulation. In subjects with PVD, retinal vessels are stiffer and more irregular, and both neurovascular coupling and autoregulation capacity are reduced while retinal venous pressure is often increased. Asymmetric glaucomatous damage was associated with lower retrobulbar hemodynamics in the eye with more advanced damage, highlighting the role of vascular factors in the progression of glaucoma[1,2]. In a four-year prospective study involving glaucoma patients, systemic vascular abnormalities significantly impacted glaucoma progression, even with well-controlled intraocular pressure. Patients with vascular comorbidities had a substantial likelihood of glaucoma deterioration, highlighting the importance of comprehensive patient management beyond intraocular pressure control[3]. In a study on vascular factors in NTG within a South Indian population, assessments included medical histories, blood pressure, lipid profiles, intraocular pressure (IOP), and central corneal thickness. Perimetry was conducted to assess visual field defects. The results highlighted a significant association between diastolic perfusion pressure and visual field defects, emphasizing the relevance of vascular factors in NTG progression. Hypertension emerged as a notable risk factor in NTG, reinforcing the pivotal role of vascular considerations in understanding this condition[4].

Various studies have demonstrated reduced blood flow in ocular and systemic vessels observed in glaucoma, leading to dysregulation. This can result in overperfusion or underperfusion, inducing oxidative stress through unstable perfusion cycles. PVD affects autoregulation, contributing to glaucomatous optic neuropathy (GON). Systemic vascular dysregulation leads to sustained reduction in ocular blood flow, affecting the choroid and optic nerve head. Overall, vascular dysregulation plays a significant role in the progression of GON[5]. In understanding the development and progression of NTG, it's crucial to acknowledge multi-level circulation-related pathologies. Early-stage NTG patients exhibit subclinical vascular abnormalities at both macro- and micro-vascular levels. This includes altered retinal vascular responses to flickering light, enhanced arterial constriction, reduced venous dilation, increased carotid intima-media thickness, and an elevated pulse wave analysis augmentation index. These findings emphasize the complex interplay of vascular factors in the early stages of NTG, providing insights for comprehensive diagnostic and therapeutic approaches [6].

THE BLOOD PRESSURE FACTOR

The Skrzypecki *et al*'s study explores in detail, the complex relationship between arterial blood pressure (ABP), IOP, and the risk of glaucoma[7]. It suggests that both low and high ABP levels may impact optic nerve health, but evidence-based guidelines for managing ABP in glaucoma patients are lacking. Notably, hypertension trials, such as the SPRINT study, have not included eye-related endpoints, missing an opportunity to investigate the effect of intensive ABP reduction on glaucoma progression and optimal antihypertensive medications. The concept of ocular perfusion pressure (OPP) is introduced to better understand the relationship between low ABP and glaucoma progression. OPP is defined as the difference between systolic blood pressure or diastolic blood pressure and IOP[7]. A number of studies have shown that a reduced OPP and increased fluctuation of OPP are risk factors for glaucoma progression. Retinal venous pressure (RVP), which refers to the blood pressure within the veins of the retina, has been commonly presumed to be equivalent to IOP in most of these studies. Meanwhile, it has been shown that in the majority of glaucoma patients, RVP is far above IOP therefore, the OPP in such cases is much lower than was previously assumed. High RVP reduces the OPP and therefore reduces circulation of both the retina and the optic nerve head (ONH). The reduction of ONH perfusion contributes to glaucomatous damage[8].

Blood pressure fluctuations play a significant role in normal-tension glaucomatous optic neuropathy. Two studies emphasize the importance of 24-h ambulatory blood pressure monitoring. The first study by Melgarejo found a strong association between blood pressure variability, particularly in mean arterial pressure readings, and the risk of GON, independent of blood pressure levels. The second study by Plange observed that patients with NTG had higher night-time diastolic and mean arterial blood pressure values and increased variability in night-time blood pressure. This increased blood pressure fluctuation may contribute to ocular perfusion pressure variations and potential ischemic episodes at the optic nerve head, linking blood pressure variability to NTG[9,10].

A recent prospective study investigated ambulatory fluctuations in IOP and blood pressure (BP) in patients with NTG. The study uncovered that many NTG patients displayed signs of vascular dysregulation, including systemic hypertension, reduced night time BP drop, and a morning BP surge. This highlights the importance of considering these vascular factors in NTG. These findings emphasize the importance of considering BP fluctuations in the context of NTG, shedding light on the broader vascular implications in glaucoma pathogenesis[11].

THE SIGNIFICANCE OF BLOOD FLOW IN NORMAL-TENSION GLAUCOMA

Two principal theories for the pathogenesis of GON have been described - a mechanical and a vascular theory. Both have been defended by various research groups over the past 150 years. The mechanical theory of glaucoma links optic nerve damage to increased IOP. However, the vascular theory suggests that GON arises from insufficient blood supply, either due to elevated IOP or other factors reducing ocular blood flow. While conditions like congenital or angle-closure glaucoma demonstrate IOP's role in GON, NTG challenges this pressure-centric view. Numerous studies in NTG patients highlight reduced ocular perfusion compared to normal subjects, implying factors beyond pressure may contribute significantly to NTG's development[12]. The exact mechanisms connecting cardiovascular disease, blood pressure, and glaucoma remain the subject of ongoing investigation. One prevailing theory is that these conditions share a common denominator: Blood vessels. Alterations in blood vessels are central to both cardiovascular disease and glaucoma. Studies indicate that glaucoma patients exhibit reduced ocular blood flow biomarkers, especially peak systolic velocity and mean flow velocity, linked to lamina cribrosa deformation. However, glaucoma suspects with similar lamina cribrosa shapes did not show this correlation, revealing a complex relationship between ocular blood flow and lamina cribrosa morphology. Vascular factors play a vital role in NTG and related conditions. Abnormal ocular blood flow detected through various imaging techniques is associated with glaucomatous optic neuropathy. Systemic disorders like migraine, systemic hypotension, Alzheimer's disease, primary vascular dysregulation, and Flammer syndrome contribute to NTG progression. Flammer syndrome, describes a phenotype characterized by primary vascular dysregulation, involves various symptoms triggered by stimuli like cold or stress. Nearly all organs, particularly the eye, can be involved. While it has protective aspects against conditions like atherosclerosis, it's also associated with diseases such as NTG[13]. Mechanisms of abnormal ocular blood flow include oxidative stress, vasospasm, and endothelial dysfunction, impacting mitochondrial function in the optic nerve head. Improving ocular blood flow may offer neuroprotective benefits in addition to lowering IOP in glaucoma treatment[14,15]. Optic nerve blood flow responses to perfusion pressure changes

were examined in individuals with NTG and controls. The study indicated no significant changes in the optic nerve blood flow in either group, but NTG patients showed a trend towards increased vascular resistance compared to controls, suggesting potential alterations in vessel tone regulation mechanisms, shedding light on the pathophysiology of NTG, which requires further investigation[16].

EXPLORING THE CONNECTION; GLAUCOMA AND SYSTEMIC FACTORS

In the realm of glaucoma, systemic factors significantly influence its development. Diabetes and elevated blood sugar levels could affect lipid metabolism, raising oxidative stress and cell apoptosis, resembling mechanisms in glaucoma-related retinal cell loss. Alterations in diabetes-related connective tissue might impact both the lamina cribrosa and potentially the trabecular meshwork, possibly influencing optic nerve biomechanics and fluid drainage, potentially raising the risk of glaucoma[17]. Diabetic retinopathy (DR) and hypertension are pivotal risk factors. Proliferative diabetic retinopathy can lead to neovascular glaucoma (NVG) with a sudden IOP surge. Hypertension raises glaucoma risk through central retinal vein occlusion, a precursor to NVG. Hypotension increases the risk to the optic nerve, causing ischemic injury and higher glaucoma risk. Carotid-cavernous fistulas disrupt IOP dynamics. The primary vascular dysregulation syndrome, often accompanied by systemic hypotension, disrupts the autoregulation of ocular blood flow. This vascular abnormality and associated autonomic dysfunction can lead to oxidative stress in glaucomatous neuropathy. Understanding these connections highlights the multifaceted nature of glaucoma and potential therapeutic interventions[18,19]. In the 2010-2012 KNHANES Survey, we used the Framingham risk score to assess the association between glaucoma and cardiovascular diseases. Regardless of the glaucoma subtype, individuals with glaucoma showed a significantly higher 10-year risk of general cardiovascular disease compared to the control group. This indicates an increased susceptibility to cardiovascular events in glaucoma patients, emphasizing the positive interplay with compromised autoregulatory capacity[20].

The examination of autonomic dysfunction, assessed through heart rate variability (HRV) as a possible factor contributing to the reduction of mean ocular perfusion pressure (MOPP), is a notable focus in two studies. These studies shed light on autonomic dysfunction and HRV in glaucoma, including NTG. Both high tension glaucoma and NTG patients exhibited reduced MOPP and lower diastolic blood pressure. HRV assessments indicated increased sympathetic innervation in glaucoma patients, particularly during a stress test, revealing autonomic disturbance in NTG patients. This disturbance is closely tied to ocular blood flow dynamics and structural damage[21,22]. Elevated sympathetic neural activity raises vascular resistance, particularly in cases of endothelial dysfunction, impacting glaucoma development. Blood supply to different organs or vascular beds is regulated by the vascular endothelium. Endothelial dysfunction can lead to inadequate organ perfusion due to vascular dysregulation, especially in individuals with a predisposition. This may result in characteristic vascular-mediated diseases such as normal-tension glaucoma[23].

MEDICATIONS AND EYE HEALTH

Certain medications have been postulated to increase the risk of development of glaucoma. Studies suggest that both high and low blood pressure can elevate the risk of developing glaucoma. While the precise mechanisms behind this connection remain unclear, it is believed to involve pathological changes in blood vessels, which are relevant in both cardiovascular disease and glaucoma. Two studies suggest a connection between cardiovascular medications and glaucoma. Commonly used medications for cardiovascular health and hypertension such as Beta-blockers, may influence blood flow to the eyes, potentially increasing the risk of glaucoma. All β -blockers lower IOP *via* inhibition of β_2 -adrenoceptors present on the ciliary epithelium, thus reducing aqueous humor flow. Beta-blockers can be classified into non-selective and selective types based on their affinity for β_1 and β_2 receptors. Non-selective β -blockers like propranolol block both β_1 and β_2 receptors, affecting not only the eye but also other organs like the heart and lungs. Selective β -blockers, such as betaxolol, predominantly target β_1 receptors and have a lesser impact on β_2 receptors in comparison to non-selective blockers (Table 1)[24].

Calcium channel blockers (CCBs) were also linked to higher glaucoma prevalence, but the causal relationship remains unclear. For glaucoma patients on systemic antihypertensive medications, these findings have important implications. A differentiation is necessary between normal doses for arterial hypertension and the significantly smaller doses used for treating vascular dysregulation. This distinction is vital considering that very low doses are employed, which minimally impact BP. CCB may have negligible BP-lowering effects in individuals with already low BP. Despite individuals with Flammer syndrome often having lower BP, some may develop high BP with age. In such instances, a cautious approach with a low-dose CCB in antihypertensive treatment is recommended[25,26].

CONCLUSION

Intriguing as this research may be, there is much yet to be uncovered regarding the relationship between cardiovascular disease, blood pressure, and the development and progression of glaucoma. NTG is not solely an IOP-dependent condition; vascular dysregulation, systemic comorbidities, and blood pressure variability contribute significantly, reduced blood flow to the optic nerve head potentially leading to ischemia and optic nerve damage, even in cases with

Table 1 Table showing the medication impact on glaucoma risk and mechanisms

Medication	Impact on glaucoma risk
Beta-blockers	<p>Influence blood flow to the eyes, potentially increasing glaucoma risk</p> <p>Lower intraocular pressure <i>via</i> inhibition of β2-adrenoceptors on ciliary epithelium, reducing aqueous humor flow</p> <p>Non-selective β-blockers (<i>e.g.</i>, propranolol) affect β1 and β2 receptors, impacting multiple organs including the eye, heart, and lungs</p> <p>Selective β-blockers (<i>e.g.</i>, betaxolol) primarily target β1 receptors, with a lesser impact on β2 receptors</p>
CCB	<p>CCB may have negligible BP-lowering effects in individuals with already low BP</p> <p>In Flammer syndrome, some may transition from low to high blood pressure with age, prompting the use of low-dose CCBs for hypertension treatment</p>

BP: Blood pressure; CCB: Calcium channel blocker.

apparently normal IOP. As further research unravels the intricate connections between these seemingly disparate health issues, individuals with a history of cardiovascular disease and varying blood pressure levels need to remain vigilant about their eye health. By elucidating subtle clues and potential associations between cardiology and NTG, we open the door to improved early diagnosis and tailored interventions, ultimately enhancing the quality of life for individuals living with NTG. Medications for cardiovascular health, including beta-blockers, may influence blood flow to the eyes and potentially increase the risk of glaucoma. Further research will provide invaluable insights into this complex relationship, potentially leading to enhanced prevention and treatment strategies.

FOOTNOTES

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Country/Territory of origin: India

ORCID number: Prasanna Venkatesh Ramesh 0000-0002-6105-8666; Arvind Kumar Morya 0000-0003-0462-119X; Shruthy Vaishali Ramesh 0000-0002-7706-1480; Aji Kunnath Devadas 0000-0002-5583-2926.

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