

Consensus panel examines clinical relevance of ocular blood flow in glaucoma

By Howard Larkin
in Boston

LOW ocular perfusion pressure, defined as blood pressure minus intraocular pressure, is associated with increased risk of open-angle glaucoma, according to statements released this year by an international consensus panel. However, its impact on individual patients is uncertain, though some clues exist as to which patients might be more vulnerable to blood pressure-related glaucoma risk, said Makoto Araie MD, PhD, professor and chairman of ophthalmology, University of Tokyo Graduate School of Medicine, Japan, and co-leader of the Global Glaucoma Network blood flow consensus panel.

Speaking at the World Glaucoma Congress, Dr Araie also reported that while drugs, both systemic and eye drops, have been shown to affect ocular blood flow, the impact of drug-induced blood flow changes on glaucoma progression has not been adequately studied and remains unclear. Convened last May in Ft Lauderdale, Florida, US, the blood flow consensus panel consisted of more than 100 glaucoma experts from all over the world. It considered the evidence of the role of impaired ocular blood flow in glaucoma; disease mechanisms leading to impaired ocular blood flow; the impact of drugs and other modifiable factors; and the relationship between glaucoma and systemic vascular diseases.

The role of blood pressure

Population-based studies across different ethnic groups have consistently found a positive correlation between systemic blood pressure and intraocular pressure, the consensus panel concluded. But the panel

found it unclear whether the level of blood pressure is a risk factor for development or progression of open-angle glaucoma in an individual patient. For example, the Blue Mountain Eye Study reported in 2004 showed a positive correlation between blood pressure and open-angle glaucoma, but the Barbados Eye Study reported in 2002 did not, Dr Araie pointed out. However, other evidence suggests that lower blood pressure may be a risk factor for patients with abnormal blood flow autoregulation, he said.

The consensus panel did conclude that low ocular perfusion pressure is a risk factor for primary open-angle glaucoma. Evidence supporting this statement includes population-based studies in the US, West Indies and Italy involving a wide range of racial and ethnic groups showing the risk of open-angle glaucoma is three to six times higher in subjects with low perfusion pressure. Nine-year results from the Barbados Eye Study found a risk ratio of nearly 3.0 for mean perfusion pressure below 40 mmHg, Dr Araie noted.

The panel also found that ocular blood flow parameters as measured by various methods are also likely to be impaired in open-angle glaucoma, particularly normal tension glaucoma. Studies show lower blood flow velocity and higher resistance indexes in both the ophthalmic artery and the central retinal artery in POAG and NTG patients compared with normal controls. Reduction of ocular blood flow with age has been shown by various methods, which may partially explain increased glaucoma incidence with age. Optic nerve head blood flow may also show nocturnal dipping in normal-tension glaucoma patients, Dr Araie added.

Vascular dysregulation as a risk factor

The panel also determined that systemic vascular dysregulation may contribute to the pathogenesis of glaucoma, more likely in people with lower intraocular pressure. It is thought that vascular dysregulation may result in defective autoregulation of ocular blood flow and instable blood supplies to tissues associated with glaucoma, Dr Araie said. One mechanism that has been implicated is endothelial dysfunction associated with endothelin-1 and NO system abnormalities. One study showed blood flow in the forearm increased less in response to blocking endothelin in patients with normal-tension glaucoma than subjects without, suggesting that the abnormal systemic blood flow response may be related to reduced ocular perfusion. Normal-tension glaucoma patients also show lower flow-mediated vasodilation in response to NO produced by endothelial cells, also suggesting ocular blood flow restrictions may be related to systemic vascular regulation problems.

Systemic factors also possibly related to unstable ocular blood flow include nocturnal blood pressure over-dipping, sleep apnoea and migraine. Suspicious and glaucomatous disc changes have been shown to occur at a higher rate in patients with sleep apnoea than in normal controls. Other, less certain, systemic indicators of increased glaucoma risk may include the presence of atrial fibrillation, atherosclerosis, haemorrhagic abnormalities or unusual ocular perfusion pressure changes related to body position, Dr Araie said.

Certain drugs, even when formulated as eye drops, may have an impact on ocular blood flow and its regulation, the panel found. Studies in monkeys have shown that even low concentrations of topically instilled drugs can penetrate at pharmacologically active levels to

the ipsilateral retrobulbar space where they can affect vessels nourishing the ocular nerve head and choroid. Dr Araie noted that more than 400 journal articles have been published on the effects of various topical drugs on ocular blood flow as measured by various methods.

Despite this, the impact of eye drop-related changes in ocular blood flow on the development and progression of glaucoma remain unknown. This may be because the effects of topical drugs, if any may be small; the studies of these drugs are relatively small-sized, and they focus on short-term effects. However, there is some evidence that carbonic anhydrase inhibitors may increase ocular blood flow and improve blood flow regulation beyond what would be expected from their intraocular pressure-reducing properties alone, he added.

A variety of systemic drugs also have been shown to affect ocular blood flow, the panel found. These include CAIs, Ca²⁺ antagonists, ACE inhibitors, angiotensin receptor inhibitors, and phosphodiesterase-5 inhibitors, Dr Araie reported. But the impact of these agents is also unknown, as no large, randomised controlled studies have been conducted to determine the effects of ocular blood flow regulation on glaucoma development or progression. The panel also found the evidence linking systemic diseases, including diabetes and cardiovascular diseases, is inconclusive.

Documents from the Global Consensus Meeting on Ocular Blood Flow and Glaucoma will be available on the WGA's website www.worldglaucoma.org and published as a hardcover book by Kugler Publications (Amsterdam, the Netherlands).

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