OCULAR BLOOD FLOW IN GLAUCOMA MANAGEMENT

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Evolution of the Definition of Primary Open-Angle Glaucoma

- Former definition
  - A disorder characterized by increased IOP that may cause impaired vision, ranging from slight loss to absolute blindness
- Current definition
  - Primary open-angle glaucoma is a multifactorial optic neuropathy in which there is a characteristic acquired loss of retinal ganglion cells and atrophy of the optic nerve

Adapted from Berkow R, Fetcher AJ, eds. *The Merck Manual of Diagnosis and Therapy*, 15th ed, 1987; Preferred Practice Pattern™. American Academy of Ophthalmology, 2000.

Slide 2

Ocular Hypertension

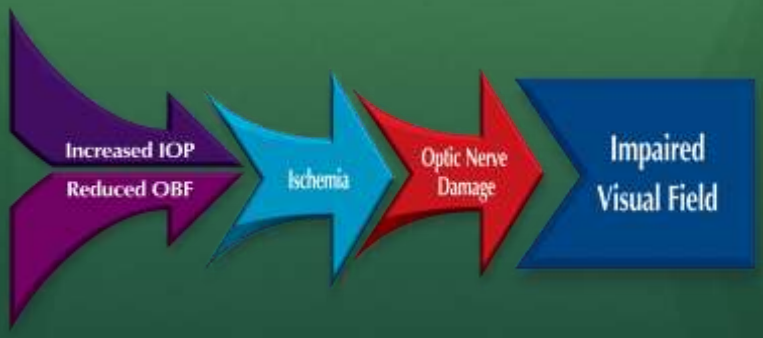
- Definition:
  - Measured IOP >21 mmHg without treatment
- Ocular Hypertension generally occurs without visual field findings and without changes to the optic disk or retinal nerve fiber layer
- The etiology and pathomechanism is unknown and risk factors have not been identified
- Although unproven, ocular HTN has been associated with vascular occlusion primarily in patients with high blood pressure, hypercholesterolemia, or obesity

European Glaucoma Society. *Terminology and Guidelines for Glaucoma*, 3rd ed. Savona, Italy: European Glaucoma Society; 2008.

Pathogenesis of glaucomatous optic neuropathy

- Mechanical theory
  - Increased intraocular pressure causes stretching of the laminar beams and damage to retinal ganglion cell axons
- Vascular theory
  - GON is a consequence of insufficient blood supply due to either increased IOP or other risk factors reducing ocular blood flow

Many factors are associated with glaucomatous damage



Adapted from Harris et al. (2005) [3]

This figure is not an exact representation of the proportional combination of the various factors leading to visual field loss. IOP=Intraocular pressure, OBF=ocular blood flow

Many factors are associated with glaucomatous damage

A comprehensive look at factors that contribute to glaucomatous damage

- While IOP is a major risk factor, glaucomatous damage still occurs in patients with controlled IOP
- Visual field damage may result from several factors, including elevated IOP and altered OBF
- Increasing age and greater IOP fluctuation increase the odds of visual field progression

Moving Beyond IOP Control

- The progression of glaucoma appears to be **multifactorial**
  - Up to 30% of newly diagnosed POAG patients may have "normal"* IOP
  - Lowering IOP alone does not always prevent progression of visual-field damage
  - Vascular factors, without elevated IOP, may lead to tissue ischemia and glaucomatous damage

Adapted from Flammer J *Glaucoma*. Bern: Verlag Hans Huber, 2001; Beers MH, Berkow R, eds. *The Merck Manual of Diagnosis and Therapy*. 17th ed. Whitehouse Station, NJ: Merck Research Laboratories, 1999; Broadway DC, Drance SM *Br J Ophthalmol* 1998;82:862-870; Drance SM et al *Am J Ophthalmol* 1998;125(5):585-592; Dielemans I et al *Ophthalmology* 1994;101:1851-1855.

Slide 7

Vascular factors are probably involved in the pathogenesis of glaucoma

- Since glaucoma patients can continue deteriorating in spite of an apparently well controlled IOP, the need for effective non-IOP related treatments is widely acknowledged
- Vascular factors are probably involved in the pathogenesis of glaucoma. Recent epidemiological studies have shown an association between low systemic diastolic blood pressure and low ocular perfusion pressure and the incidence, prevalence and progression of glaucoma
- At the present time the clinical role of blood flow measurements in glaucoma management is unclear. Clinical vascular risk factors should be taken into account in glaucoma management especially when the IOP is low over 24 hours with normal CCT and visual fields show severe and progressive alteration

European glaucoma society guidelines

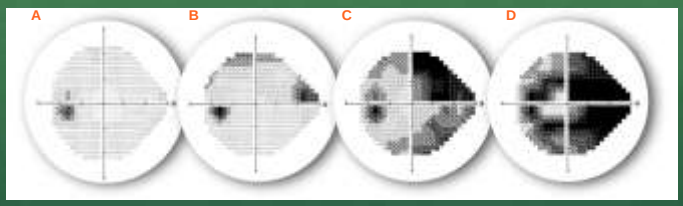
How to test OBF

- Color Doppler Imaging
- Scanning Laser Doppler Flowmetry

Color Doppler Imaging

- Ophthalmic artery (OA) flow measurement
- Short posterior ciliary artery (SPCA) measurement
- Central retinal artery (CRA) measurement
- Peak systolic velocity(PSV) and end-diastolic velocity(EDV) were measured in the above vessels
- Resistivity index(RI) was then calculated through the following formula RI=PSV-EDV/PSV (Pourcelot)

Visual field test showing progressive vision loss in a glaucoma patient over time



- **A** Normal visual field
- **B** Loss of visual field in the superior and nasal portion
- **C** Visual field loss extends to superior and inferior portions of vision
- **D** Advanced disease with extensive damage to entire visual field

Adapted from Distelhorst et al. (2003) [2]

Computerized visual field analysis demonstrating progressive visual field loss in the left eye of a patient with uncontrolled glaucoma.
Images used with permission from Lisa Rosenberg MD, University Eye Specialists, Chicago, Illinois, USA.

Glaucoma: Treatment Goal

The goal of glaucoma treatment is to maintain the visual function and related quality of life at a sustainable cost

Terminology and guidelines of glaucoma 4th edition

Slide 12

Treatment of glaucoma

- Currently, the only approach proven to be efficient in preserving visual function is lowering IOP.
- Other possible treatment areas have been investigated including ocular blood flow.
- There are experimental as well population studies indicating that perfusion pressure may be relevant in glaucoma.
- Also a specific glaucoma phenotype characterised by vascular dysregulation has been described.

Treatment of glaucoma

- Lowering the IOP
  - Medical
  - Laser
  - Surgery

First line drugs

- Prostaglandin analogues
- Beta receptor antagonists
- Carbonic anhydrase inhibitors
- Alpha-2 selective adrenergic agonists

Second line drugs

- Non selective adrenergic agonists
- Parasympathomimetics
- Osmotics

Dorzolamide

- Previous studies have shown the ocular haemodynamic effects of topically applied dorzolamide

- Galassi et al .2002
- Martinez and Sanchez 2008

Dorzolamide and Timolol

- Martinez and Sanchez observed patients with POAG followed for 60 months and studied ocular blood flow and found the following:
  - Significant increase from the baseline in mean EDV values
  - Significant reduction in mean RI in all retrobulbar vessels
  - Both will lead to increase in OBF

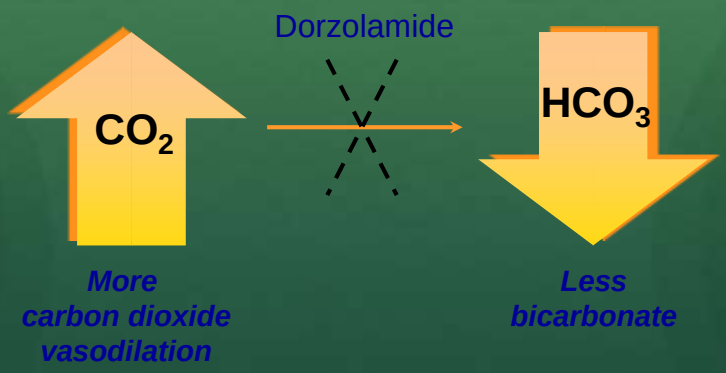
- ACTA OPHTHALMOLOGICA 2010

DTFC

- One year treatment with LTFC and DTFC showed similar IOP lowering effects as well as stable visual function. The DTFC showed lower resistance in retrobulbar vessels

- Eur J Ophthalmol 2009

Topical CAIs: Inhibition of Carbonic Anhydrase



Adapted from Harris A, Jonescu-Cuypers CP *Curr Opin Ophthalmol* 2001;12:131-137.

Concept Definitions

- **Compliance**: extent to which a patient takes a prescribed medication
  - "Yes, I am taking my medication."
- **Adherence**: extent to which a patient self-administers medication exactly as prescribed
  - "Yes, I am taking my medication as prescribed, the correct number of drops in the correct eye, at the correct time of day."
- **Persistence**: length of time over which a patient continues to take a medication
  - "Yes, I have been taking my medication for the past 6 months as prescribed."
- CAP=**Compliance**, **Adherence**, **and Persistence**

Slide 21

Compliance, Adherence, and Persistence

- Importance of Controlling IOP
  - Poor adherence is significantly associated with development of blindness in patients with open-angle glaucoma
  - In patients with advanced glaucoma, reduction of IOP from >17.6 mmHg to <14 mmHg significantly (*P*=0.002) reduced additional damage to the optic nerve

Kass MA et al. *Arch Ophthalmol.* 2002;20:701–713; Chen PP. *Ophthalmology.* 2003;110:726–733

Slide 22

Patient Compliance

- Causes of non compliance
  - Asymptomatic, preventive in nature
  - Chronic disease requiring long term therapy
  - Benefit of treatment not apparent
  - Several medications
  - Expense of treatment
  - Inconvenience of treatment
  - Local side effects of treatment
  - Systemic side effects of treatment

J of Glaucoma *1992; 1: 134-136*

Slide 23

Overview of Findings From Recent Studies

- Adherence in glaucoma patients ranges from 40% to 77%
- Findings from a recent survey of 500 ophthalmologists and their patients
  - Most ophthalmologists believed that only <25% of their patients were noncompliant, but 34% of patients reported themselves to be noncompliant

Deokule S et al. *Ophthalmic Physiol Opt.* 2004;24:9–15; Gurwitz JH et al. *Am J Public Health.* 1993;83:711–716; Patel SC et al. *Ophthal Surg.* 1995;26:233–236; Konstas A et al. *Eye.* 2000;14:752–756; Rotchford A et al. *Eye.* 1998;12:234–236; Stewart WC et al. *J Ocul Pharmacol Ther.* 2004;20:461–469.

Slide 24

Factors That Influence Adherence/Compliance

Medication-Related Factors

- Dosing >2 times daily
- Multiple bottles of topical medications for high IOP
- Medications for comorbid conditions
- Drug-related adverse experiences
- Cost
- Complexity of regimen
- Changes in regimen

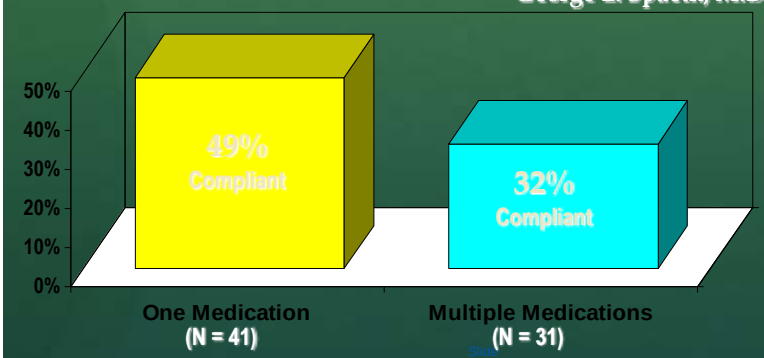
Patient-Related Factors

- Personal
  - Knowledge/skill
  - Memory
  - Motivation
  - Comorbid disease
  - Physical disabilities
  - Age
- Situational/Environmental
  - Support
  - Major life events
  - Travel/away from home
  - Competing activities
  - Change in routine

Gurwitz JH et al. *Am J Public Health.* 1993;83:711–716; Patel SC et al. *Ophthal Surg.* 1995;26:233–236; Tsai JC et al. *Glaucoma.* 2003;12:393–398.

Compliance Challenges

"...in the long run, single drugs that do the work of more than one drug...likely would enhance compliance."
- George L. Spaeth, M.D.



Patel SC, Spaeth GL. Compliance in patients prescribed eyedrops for glaucoma. Ophthalmic Surg. 1995;26(3):234-236

ADVANTAGES OF FIXED COMBINATIONS

- Convenience
  - No need to wait between drops
  - No risk of washout effect
- Simple regimen → improved compliance
- Less exposure to preservatives
  - Benzalkonium chloride BAK
- Possible cost savings

Thank you for your attention