

Senkung des erhöhten Venendruckes

114. DOG-Kongress, 30. September 2016

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I declare not having any financial interest in marketing or selling any of the products described in this presentation.

Between June 2011 and 2015, Prof. Josef Flammer and myself were owner of the exploitation right of Patent WO 96/32884 and US Patent 6,027,454 “Ophthalmometry” originally proposed by Dr. Loew, Germany.

Research Grant: LHW Foundation, Triesen/Lichtenstein

Klinische Behandlungsanwendungen bei erhöhtem retinalem Venendruck (RVP):

- **Nifedipin Retard 5mg** (Adalat, Bayer)*
- **Magnesium 10 – 20 mmol** (300 - 500mg)*
- **Macitentan 10mg** (Opsumit, Actelion)**

* Bei POAG und primär vaskulärer Dysregulation (Flammer-Syndrom) : Auszug aus "Nahrungsmittel zur Unterstützung der Glaukomtherapie bei Patienten mit vaskulärer Dysregulation", Universitätsspital Basel

** Pilotstudie bei Hypoxie bedingtem erhöhtem RVP (Diavolezzastudie 2014)

Erhöhter retinaler Venendruck ist publiziert bei:

- Glaucoma (*Pillunat et al. 2014; Fang et al. 2014; Morgan et al. 2009; Jonas, Harder 2003*)
- Vein occlusion (*Mozaffarie et al. 2014; Yasuda et al. 2010; Jonas et al. 2007*)
- Flammer Syndrome (*Fang et al. 2014*)
- Diabetes (*Cybulska et al. 2015*)
- Hypoxia - high altitude induced (*Baertschi et al. 2016*)
 - and potentially in temporary Amaurosis (*Baertschi, ISMM 2014*)
 - retinal Hemorrhages and Optic Nerve Head Edema
(multiple 1975-2009)

Die Folgen des verringerten okulären Perfusionsdruckes
als Resultat des erhöhten retinalen Venendruckes:

- “Ungenügende okuläre Perfusion der Netzhaut verursacht eine Mangeldurchblutung und führt zu einem Sauerstoffmangel im Gewebe, welches wiederum schädliche, das Sehen bedrohende Effekte auslöst.”

Arjamaa, O. and M. Nikinmaa, Oxygen-dependent diseases in the retina: role of hypoxia-inducible factors. Exp Eye Res, 2006. 83(3): p. 473-83.

Risk Factors for Incident Open-angle Glaucoma

The Barbados Eye Studies 2008

M. Cristina Leske, MD, MPH,^{1,2} Suh-Yuh Wu, MA,^{1,2} Anselm Hennis, FRCP(UK), PhD,^{1,3,4}
Robert Honkanen, MD,² Barbara Nemesure, PhD,^{1,2} BESS Study Group

Leske et al · Risk Factors for Incident Open-angle Glaucoma: The Barbados Eye Studies

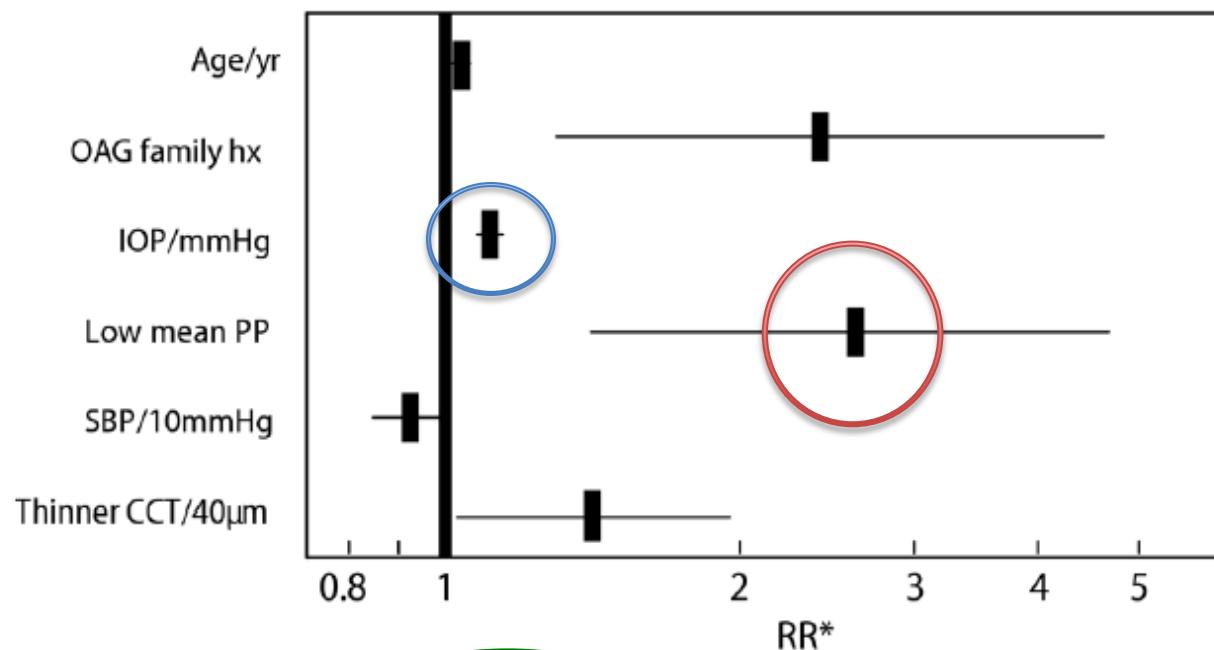


Figure 1. Risk factors for definite open-angle glaucoma (OAG; n = 3222). hx = history; PP = perfusion pressure; RR = risk ratio; SBP = systolic blood pressure. *Based on Cox regression models, adjusting for age, gender, intracocular pressure (IOP), and IOP- and blood pressure-lowering treatment; central corneal thickness (CCT) is presented as an odds ratio, based on logistic regression model in a subsample (n = 1023).

“Perfusionsdruck ist definiert als die Differenz zwischen arteriellem und venösem Blutdruck und ist die treibende Kraft des Blutflusses.”

Schmidl, D., G. Garhofer, and L. Schmetterer, The complex interaction between ocular perfusion pressure and ocular blood flow - relevance for glaucoma. Exp Eye Res, 2011. 93(2): p. 141-55.



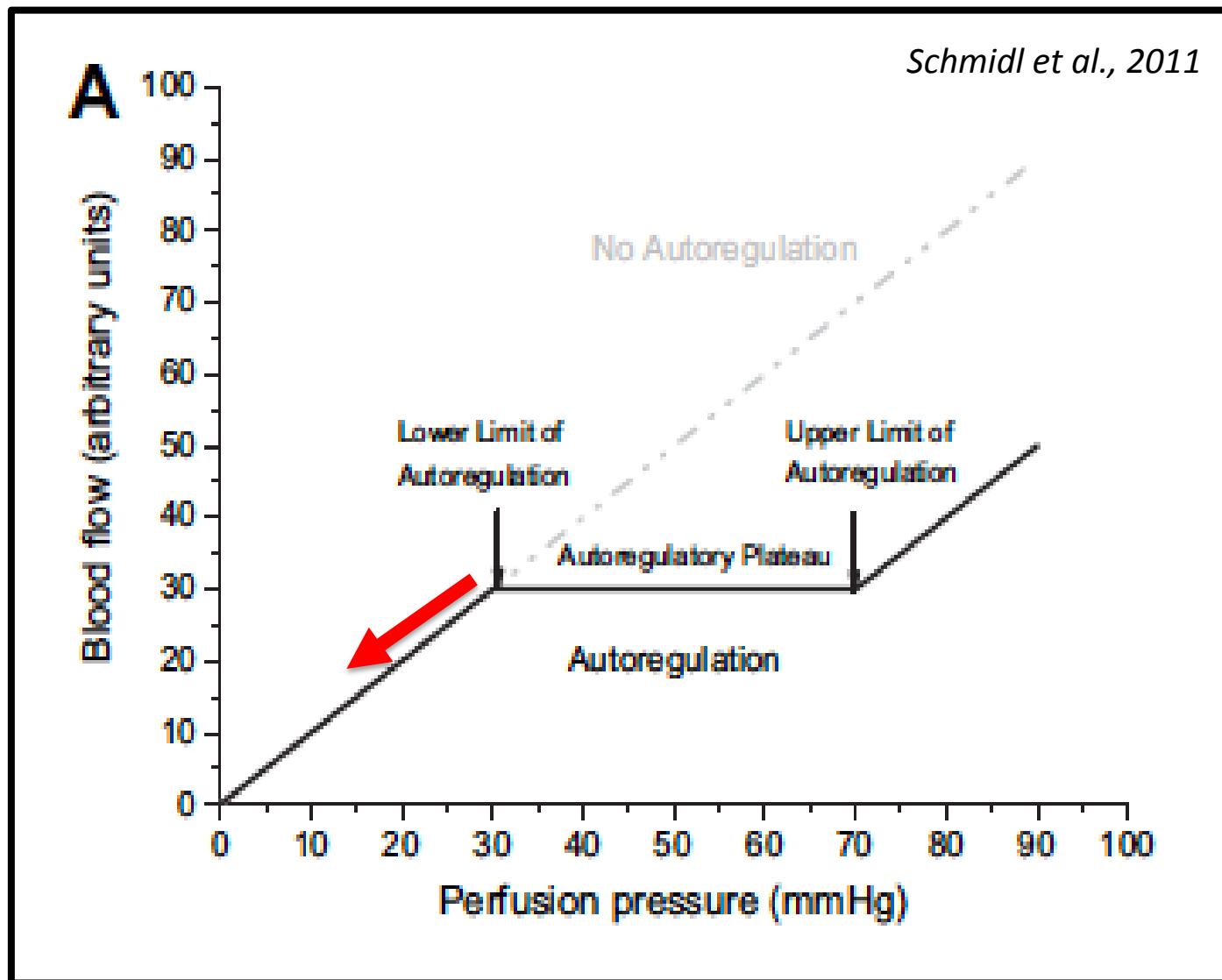
“The current state-of-the-art dynamic device”

Morgan et al. Greafes Arch Clin Exp Ophthalmol, 2010; 248(3):401-7

Ophthalmo-Dynamometry by Dr. Bernhard Loew, Germany

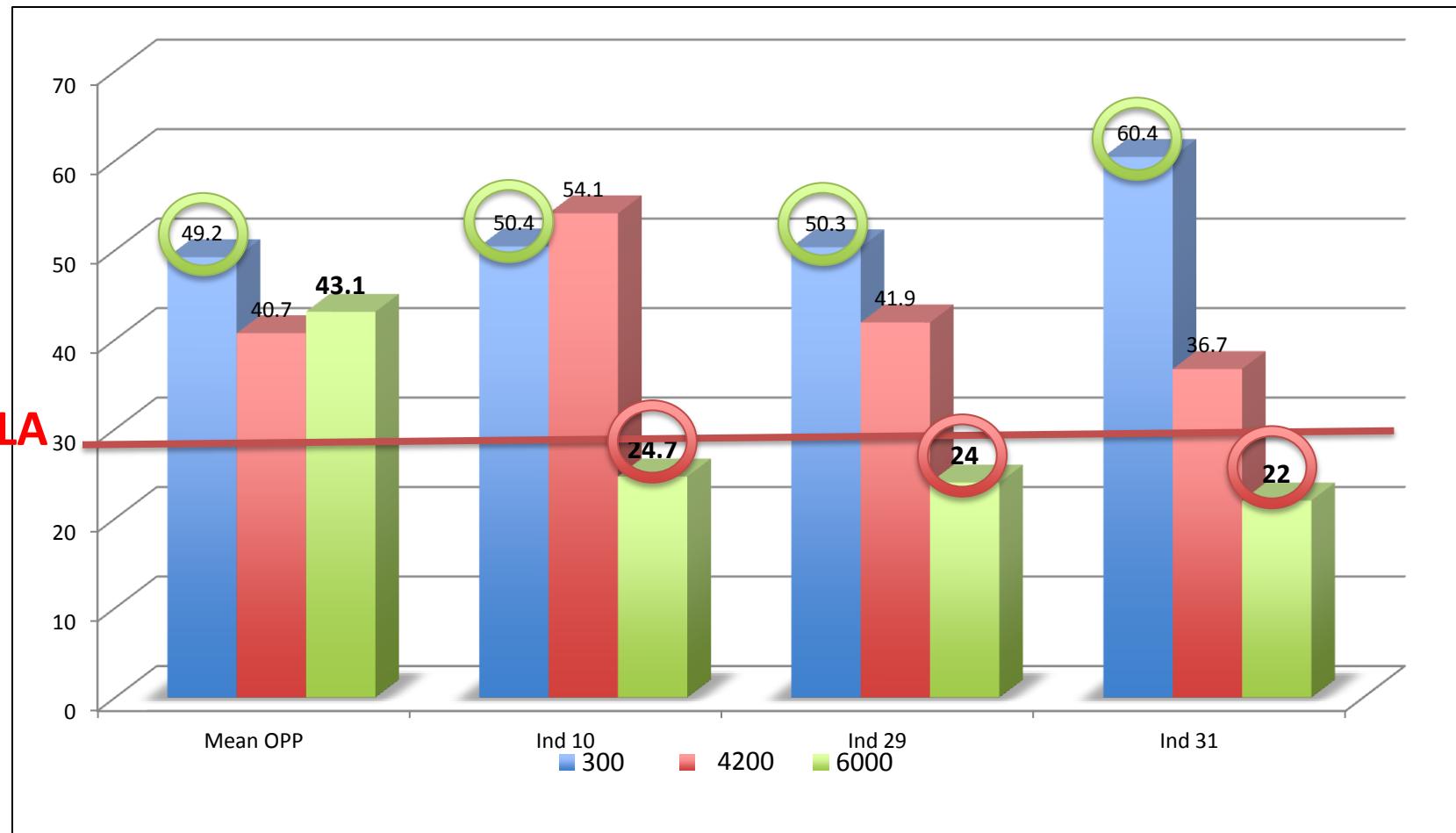
Tissue	Function and characteristics	Involved cell or fiber layer															
Retina	<p>Autoregulation</p> <p>e.g. Flicker, IOP/ICP, Endothelin-1</p> <p>Low flow rate</p> <p>Low perfusion rate</p> <p>Low venous oxygen saturation</p> <p>High vascular resistance</p> <p>High oxygen extraction</p>	<p>Inner limiting membrane</p> <p>Optic nerve fibers</p> <p>Ganglion layer</p> <p>Outer nuclear layer</p>															
Choroidea	<p>No Autoregulation</p> <p>Very high flow rate</p> <p>High perfusion rate</p> <p>Very high venous oxygen saturation</p> <p>Low vascular resistance</p> <p>Low oxygen extraction</p>	<p>The graph illustrates the relationship between blood flow and perfusion pressure for two tissues. The Y-axis represents 'Blood flow (arbitrary units)' ranging from 0 to 100. The X-axis represents 'Perfusion pressure (mmHg)' ranging from 0 to 100. A solid black line represents the Retina, showing a horizontal plateau at approximately 30 arbitrary units of blood flow between 30 and 70 mmHg, which is labeled as 'Autoregulation'. The area under this curve is shaded orange. Above this range, the blood flow increases linearly, labeled as 'No Autoregulation'. A dashed blue line represents the Choroidea, showing a continuous linear increase in blood flow as perfusion pressure increases, labeled as 'No Autoregulation'.</p> <table border="1"> <caption>Data points estimated from the graph</caption> <thead> <tr> <th>Perfusion pressure (mmHg)</th> <th>Retina Blood flow (arbitrary units)</th> <th>Choroidea Blood flow (arbitrary units)</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>0</td> <td>0</td> </tr> <tr> <td>30</td> <td>30</td> <td>30</td> </tr> <tr> <td>70</td> <td>30</td> <td>70</td> </tr> <tr> <td>100</td> <td>100</td> <td>100</td> </tr> </tbody> </table>	Perfusion pressure (mmHg)	Retina Blood flow (arbitrary units)	Choroidea Blood flow (arbitrary units)	0	0	0	30	30	30	70	30	70	100	100	100
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100	100	100															

- Riva, C.E., et al., *Autoregulation of human optic nerve head blood flow in response to acute changes in ocular perfusion pressure*. Graefes Arch Clin Exp Ophthalmol, 1997. **235**(10): p. 618-26.
- Riva, C.E., S.D. Cranstoun, and B.L. Petrig, *Effect of decreased ocular perfusion pressure on blood flow and the flicker-induced flow response in the cat optic nerve head*. Microvasc Res, 1996. **52**(3): p. 258-69.



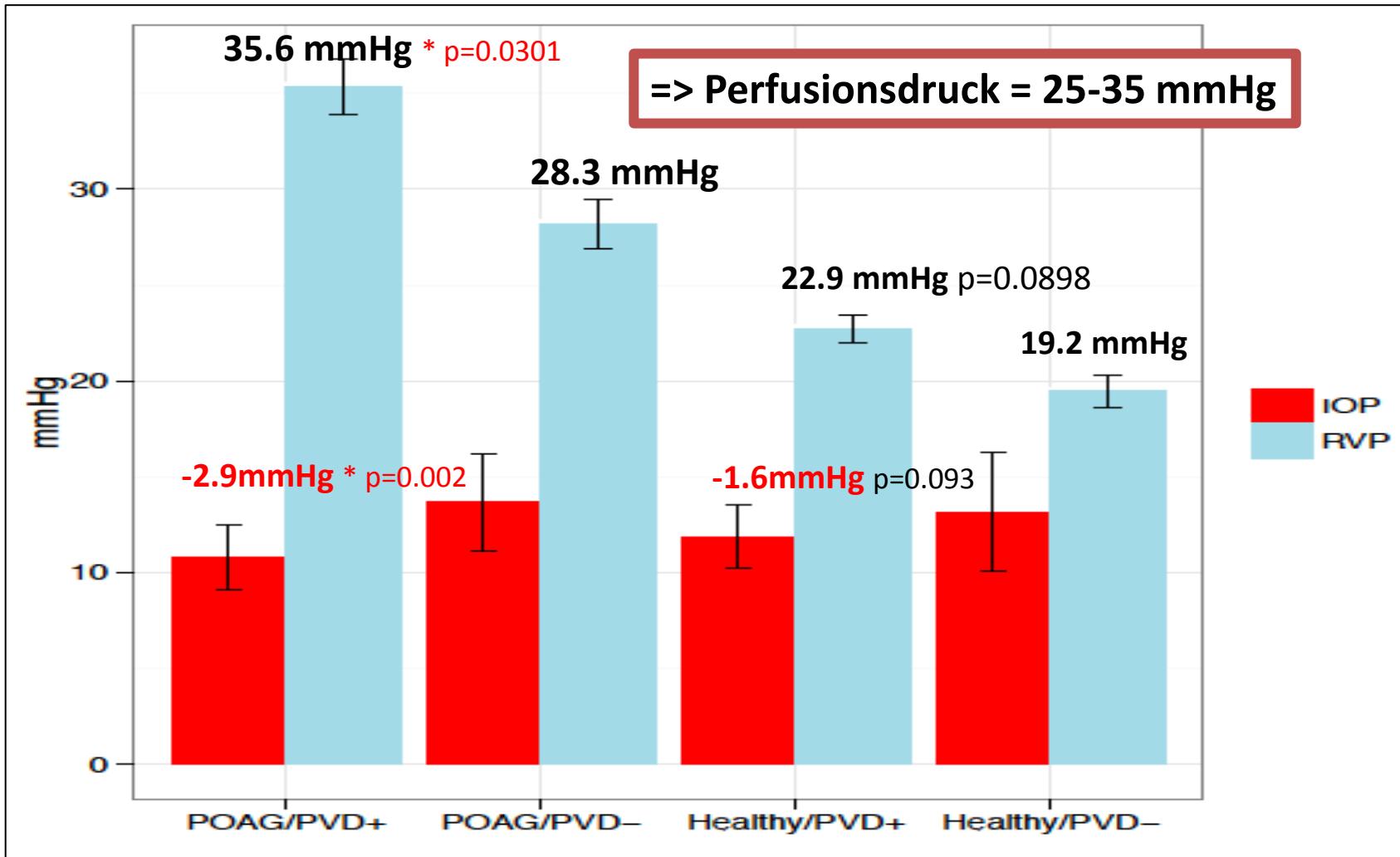
Minderung des Blutflusses um 25% bis >30%

At or below Lower Limit of Blood Flow Autoregulation in Optic Nerve Head



Baertschi, M., et al.: "The effect of hypoxia on intra-ocular, mean arterial, retinal venous and ocular perfusion pressures." Clin Hemorheol Microcirc. Vol.63, no.3, pp 239-303, 2016

IOP and RVP for POAG FS+/FS- and Healthy FS+/FS- (n=30/30)



Value of non-IOP lowering therapy for glaucoma:

Cybulska-Heinrich et al., Klin Monbl Augenheilk 2013; 230(2); 114-19

www.flammer-syndrome.ch

HOME EN DE

Flammer Syndrome

DEFINITION

TERMINOLOGY

LIFESTYLE DISEASES

NORMAL TENSION GLAUCOMA

THERAPY

LITERATURE

LINKS

HISTORY

CONTACT

THERAPY FOR FLAMMER SYNDROME

Flammer syndrome is mostly harmless, and therefore, most subjects require no treatment. However, if the symptoms are annoying or affected individuals develop related diseases, we consider treatment as necessary. The intensity of the treatment depends on the clinical picture and the individual situation. Although no large-scale study has been conducted on treatment, we can still assist these patients based on our experience. Treatment is based on three pillars: (a) lifestyle management, (b) dietary intervention, and (c) pharmacological treatment.

Lifestyle management
Most patients with Flammer syndrome complain about nocturnal blood pressure dips. Therefore, eating enough to avoid excessive nocturnal blood pressure dips. Omega-3 fatty acids, as well as magnesium, are also recommended. Since oxidative stress, induced by the unstable oxygen supply, may increase, particularly in the eye, antioxidative diet is considered.

Drug treatment
Magnesium, a physiological calcium channel blocker (CCB), reduces the vasoconstrictive effect of endothelin-1 and improves BF regulation. A relatively high dose of at least 10–20 mmol/day magnesium is needed. The only side effect observed is diarrhea, which mitigates quickly when the dose is reduced. If not sufficient, then magnesium is combined with a very low dose (!) of calcium channel blockers. But it must be done only with a doctor's prescription. Many other substances are currently under investigation. Ginkgo biloba (figure below) has already been proved effective.

Empfehlung: Magnesium 10-20mmol / Tag
Nifedipine 5 mg / Tag



Graefe's Archive for Clinical and Experimental Ophthalmology

June 2015, Volume 253, Issue 6, pp 935–939

The effect of nifedipine on retinal venous pressure of glaucoma patients with the Flammer-Syndrome

L. Fang, S. Turtschi, Maneli Mozaffarieh 

Results: **The RVP decreased significantly** after 3 weeks in both eyes of patients **treated with low-dosed Nifedipine** compared to the untreated group (mean **decrease of 12.5 mmHg** (SD 12.5), $P < 0.001$). A **larger response** to therapy was found in **patients with FS** compared to patients lacking the FS (mean decrease 14.3 mmHg (SD 12.5), $P < 0.001$). The mean IOP was 16.5 mmHg (CI): 5.2 to 9.3 vs. 12.3 to 13.8 mmHg (CI): 5.2 to 9.3. No significant differences were accounted for in the IOP's of the patients after treatment. In the untreated control group, no significant differences were accounted for either in the RVP or the IOP after 3 weeks.

Empfehlung: Nifedipine 5mg / Tag

Conclusions: **Treatment with low-dosed Nifedipine decreases RVP in both eyes of glaucoma patients, particularly in those with the Flammer-Syndrome.** This effect may be due to the partial inhibition of **Endothelin-1 (ET-1)** by Nifedipine.

- Increased plasma Endothelin- 1 level is a common denominator of several ocular diseases such as **glaucoma** ⁽¹⁾, **diabetic retinopathy** ⁽²⁾ or **retinal vein occlusion**⁽³⁾ and systemic syndromes such as **Flammer Syndrome** ⁽⁴⁾ or **systemic Hyoxia** ⁽⁵⁾.
- ET-1 acts as strong vasoconstrictor on vascular smooth vessels.

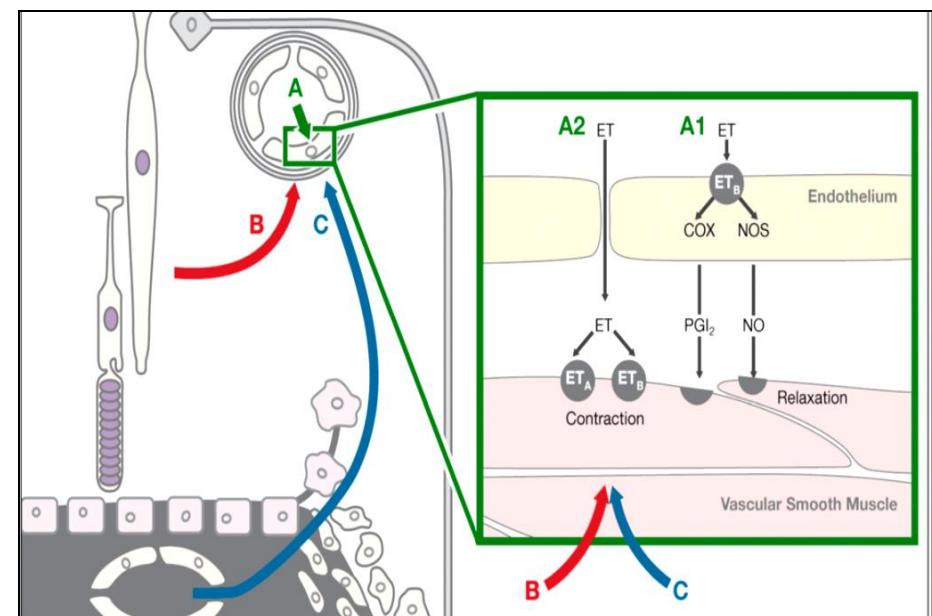
(1) Cellini, M. et al. 2012; Kaiser, H. et al. 1995

(2) Ergul, A. 2011; Kalani, M. 2008; Lam, H. et al. 2003

(3) Iannaccone, A. et al. 1998

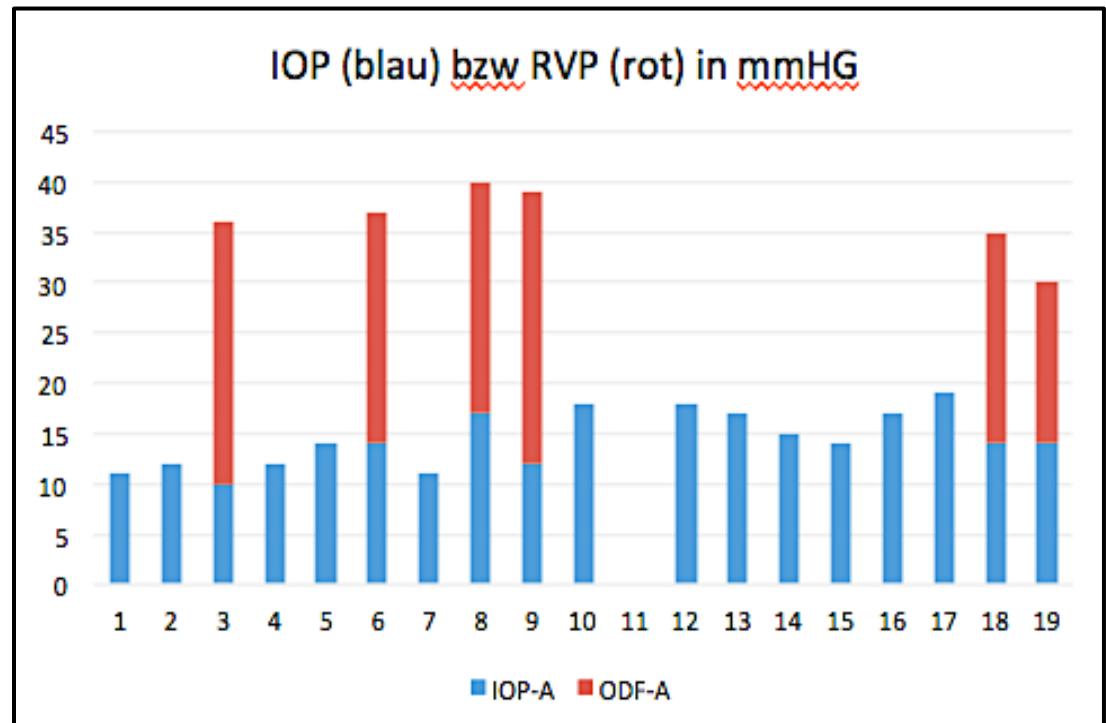
(4) Flammer, J. et al. 2013,

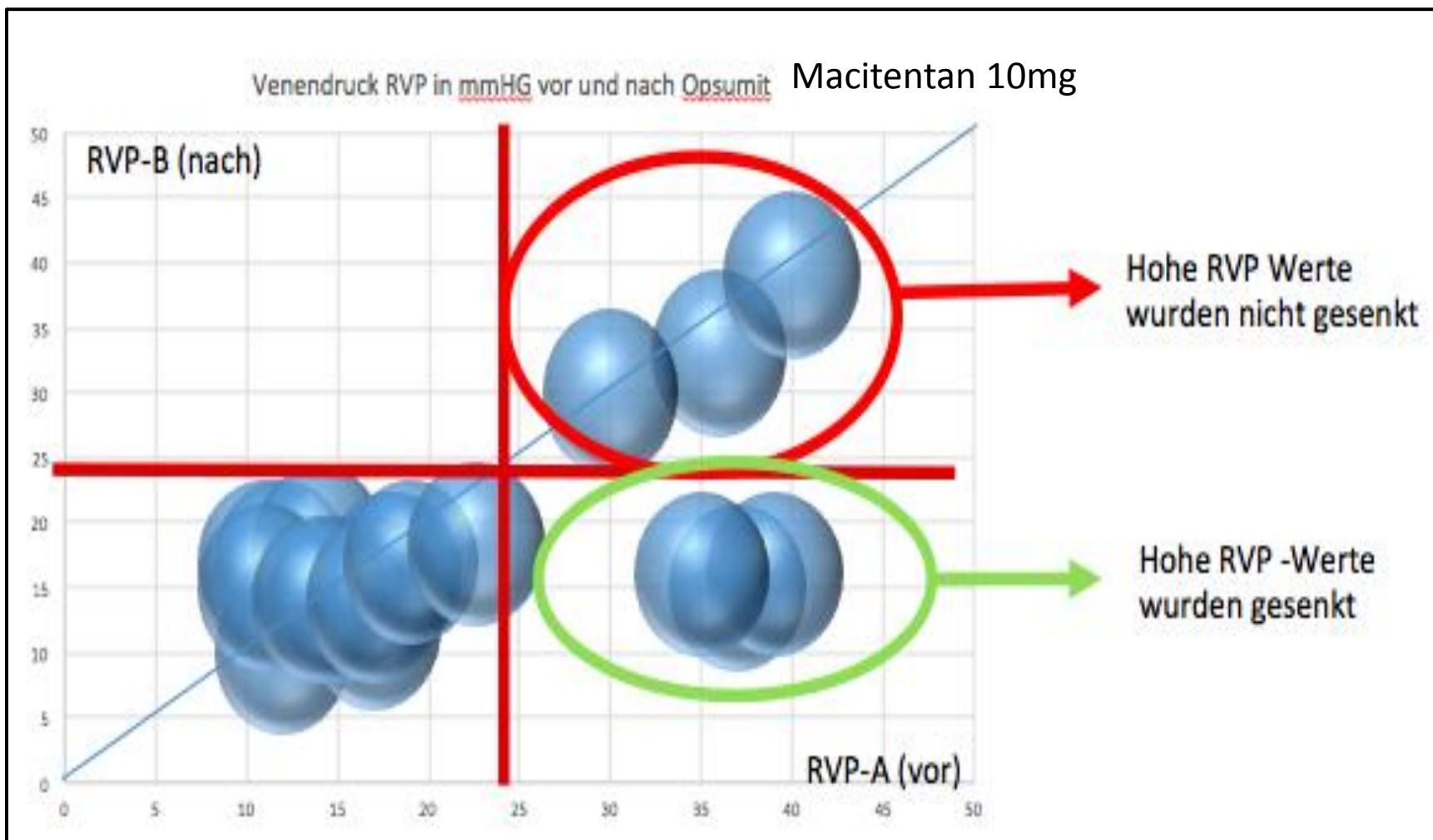
(5) Modesti, P. et al. 2006; Morganti, A. et al. 1995



Diavolezza Studie durch das Universitätsklinikum Jena

(3'000 müM, Okt. 2014)





Retinal vessel regulation at high altitudes¹

Article type: Research Article

Authors: Neumann, Thomas^{a,*} | Baertschi, Michael^{b,c} | Vilser, Walthard^d | Drinda, Stefan^e | Franz, Marcus^f | Brückmann, Andreas^g | Wolf, Gunter^a | Jung, Christian^h

[Clinical Hemorheology and Microcirculation, vol. 63, no. 3, pp. 281-292, 2016](#)

CONCLUSIONS: Retinal arterial and venous vessels react to Normobaric Hypoxia

and Hypobaric Hypoxia with a diameter increase and an impaired response to

flicker light. **Macitentan was capable to normalize the increased retinal**

venous pressure observed at high altitudes.

- Der retinale Venendruck lässt sich medikamentös klinisch signifikant senken. ^(1, 2)
- Es bestehen mit Nifedipin und Magnesium jahrelang klinisch erprobte Tx Ansätze. (Universität Basel, Prof. Flammer)
- Evidenz für ET-1 Blocker als zukünftige Therapie ist gegeben. ⁽²⁾
 - *Weitere klinische Multizenterstudien sind notwendig bezüglich optimierter Dosierung bei unterschiedlichen Krankheitsbildern.*
 - *Weitere pharmakologische Entwicklungen sind notwendig zur Erweiterung der Therapiebreite.*

1) Fang L., Turtschi S., Mozaffarieh, M.: The effect of nifedipine on RVP of glaucoma patients. *Graefes Arch Clin Exp Ophthalmol* 2015;253(6):935

2) Neumann, T., et al.: Retinal vessel regulation at high altitudes. *Clin Hemorheol Microcirc*, 2016; 63(3):281

Acknowledgments

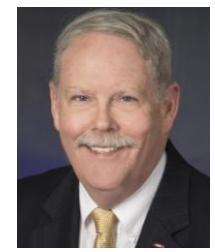
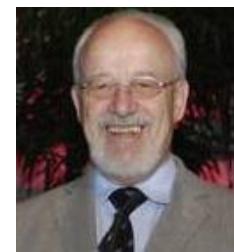
Mentors Thesis:

- **Prof. Josef Flammer**
- **Prof. Pierrette Dayhaw-Barker**



Consultants:

- Prof. Barbara Kergoat
- **Prof. Richard Stodtmeister**
- Prof. Felix Barker
- PD Dr. Maneli Mozaffarieh
- Dr. Katarzyna Konieczka



University Hospital Basel / Switzerland

- Ethic Committee Basel (EKBB)
- University Eyeclinic Basel and staff
- Study patients and subjects: > 310
- Dr. Denis Bron Air Force Medical Center (FAI)
- LHW Foundation (Grant)

