Senkung des erhöhten Venendruckes

114. DOG-Kongress, 30. September 2016

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Declaration

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

Clinical Pearls

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)*

Clinical Evidence

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)

Clinical evidence

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

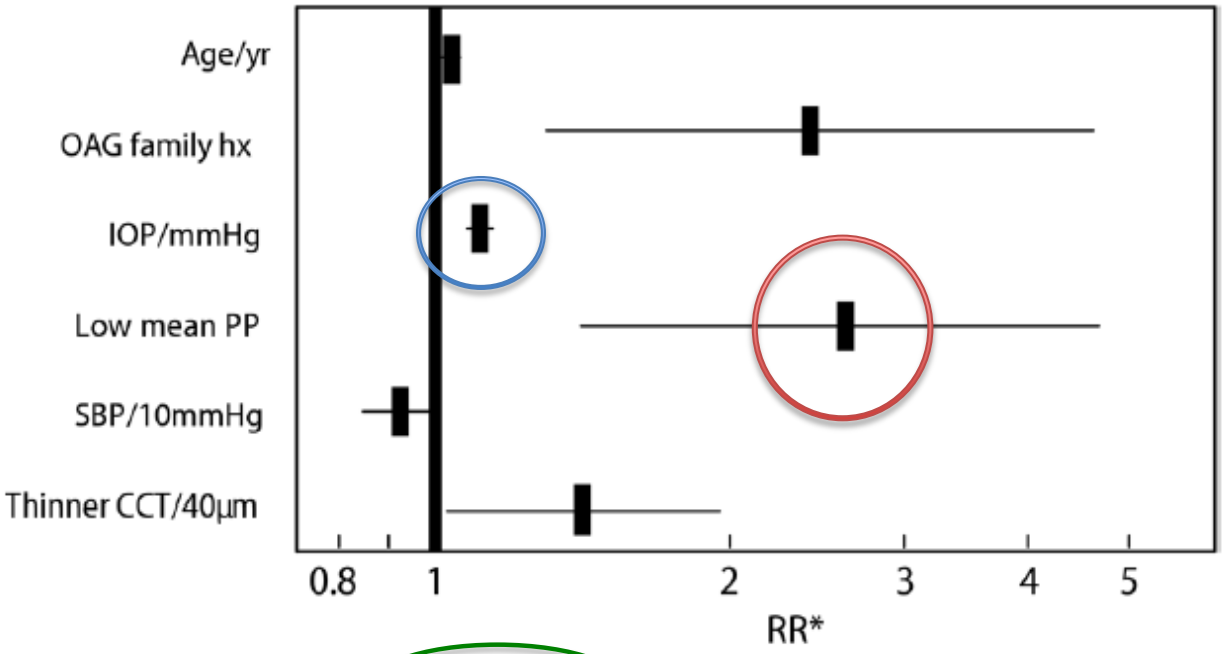


Figure 1. Risk factors for definite open-angle glaucoma (OAG; n = 3222). hx = history; PP = perfusion pressure; RR = risk ratio; SBP = systolic blood pressure. *Based on Cox regression models, adjusting for age, gender, intraocular pressure (IOP), and IOP- and blood pressure–lowering treatment; central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

Role of Perfusion Pressure

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

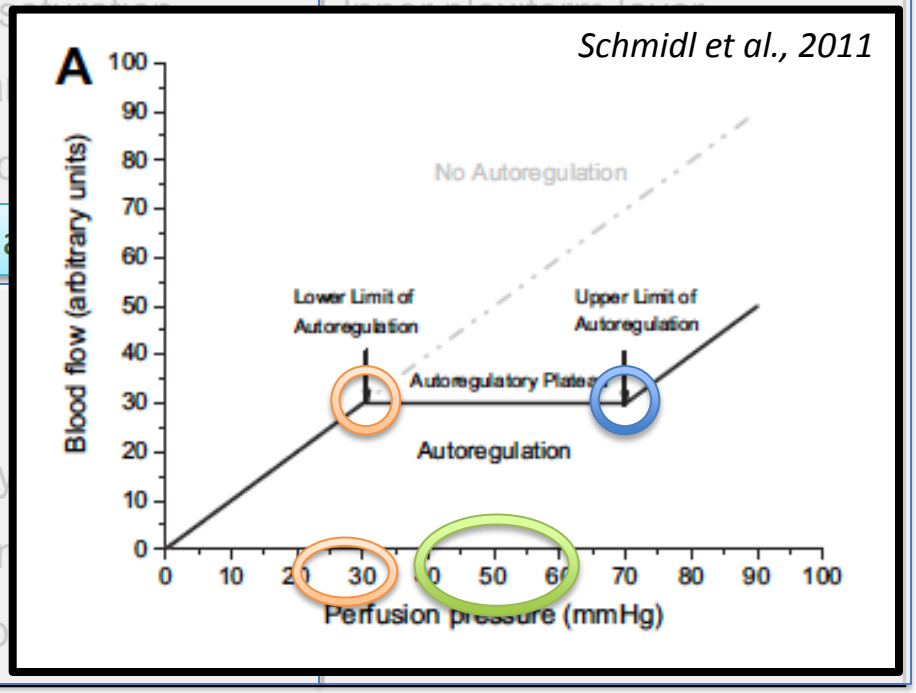
Schmidl, D., G. Garhofer, and L. Schmetterer, The complex interaction between ocular perfusion pressure and ocular blood flow - relevance for glaucoma. Exp Eye Res, 2011. 93(2): p. 141-55.

Methods and Instruments

Ophthalmo-Dynamometry by Dr. Bernhard Loew, Germany

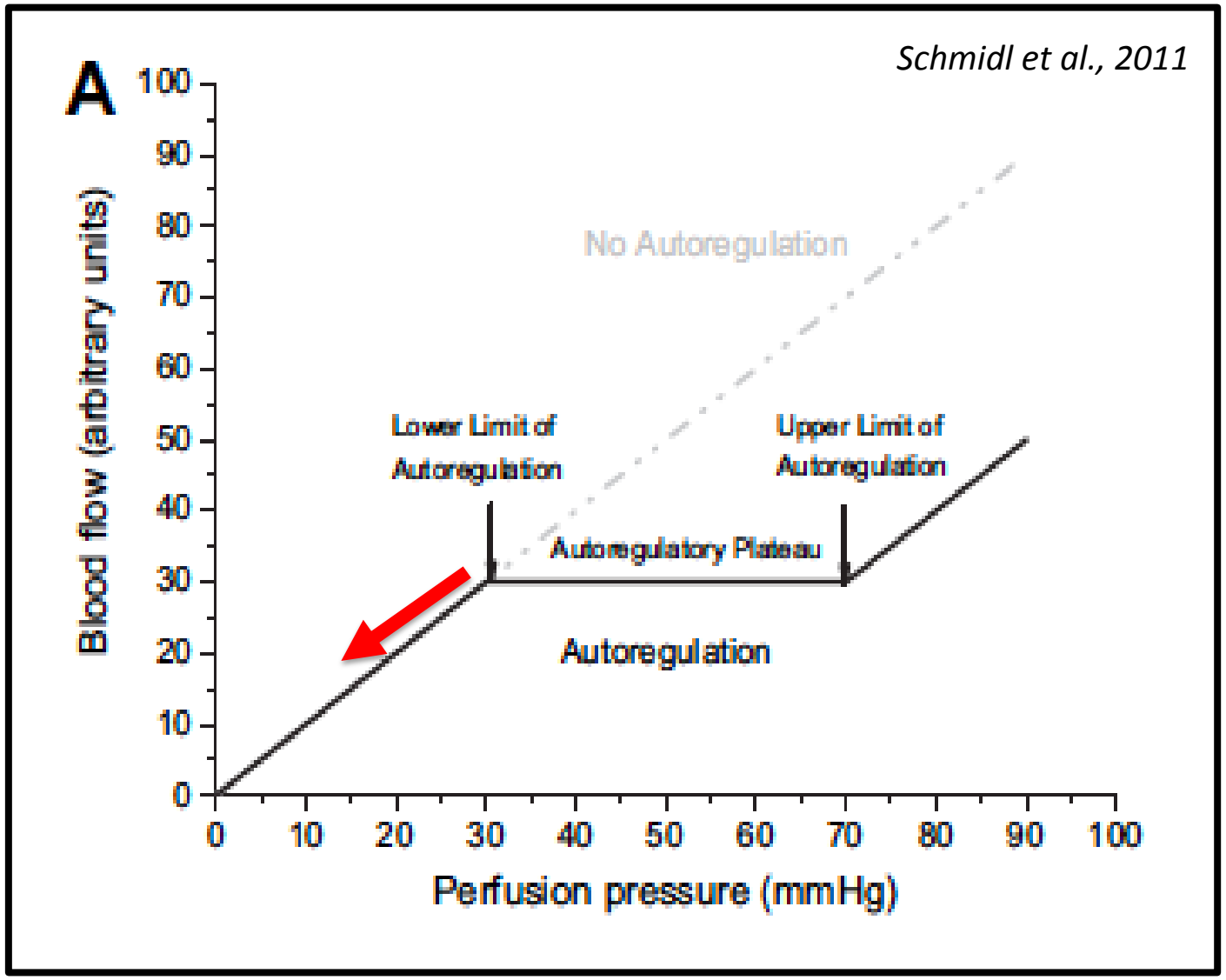
Retinal versus choroidal blood flow

Tissue	Function and characteristics	Involved cell or fiber layer
Retina	Autoregulation	Inner limiting membrane
	e.g. Flicker, IOP/ICP, Endothelin-1	Optic nerve fibers
	Low flow rate	Ganglion layer
	Low perfusion rate	
	Low venous oxygen s	
	High vascular resista	
	High oxygen extracti	
Choroidea	No Autoregulation	
	Very high flow rate	
	High perfusion rate	
	Very high venous oxy	
	Low vascular resistar	
	Low oxygen extractio	



- 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.

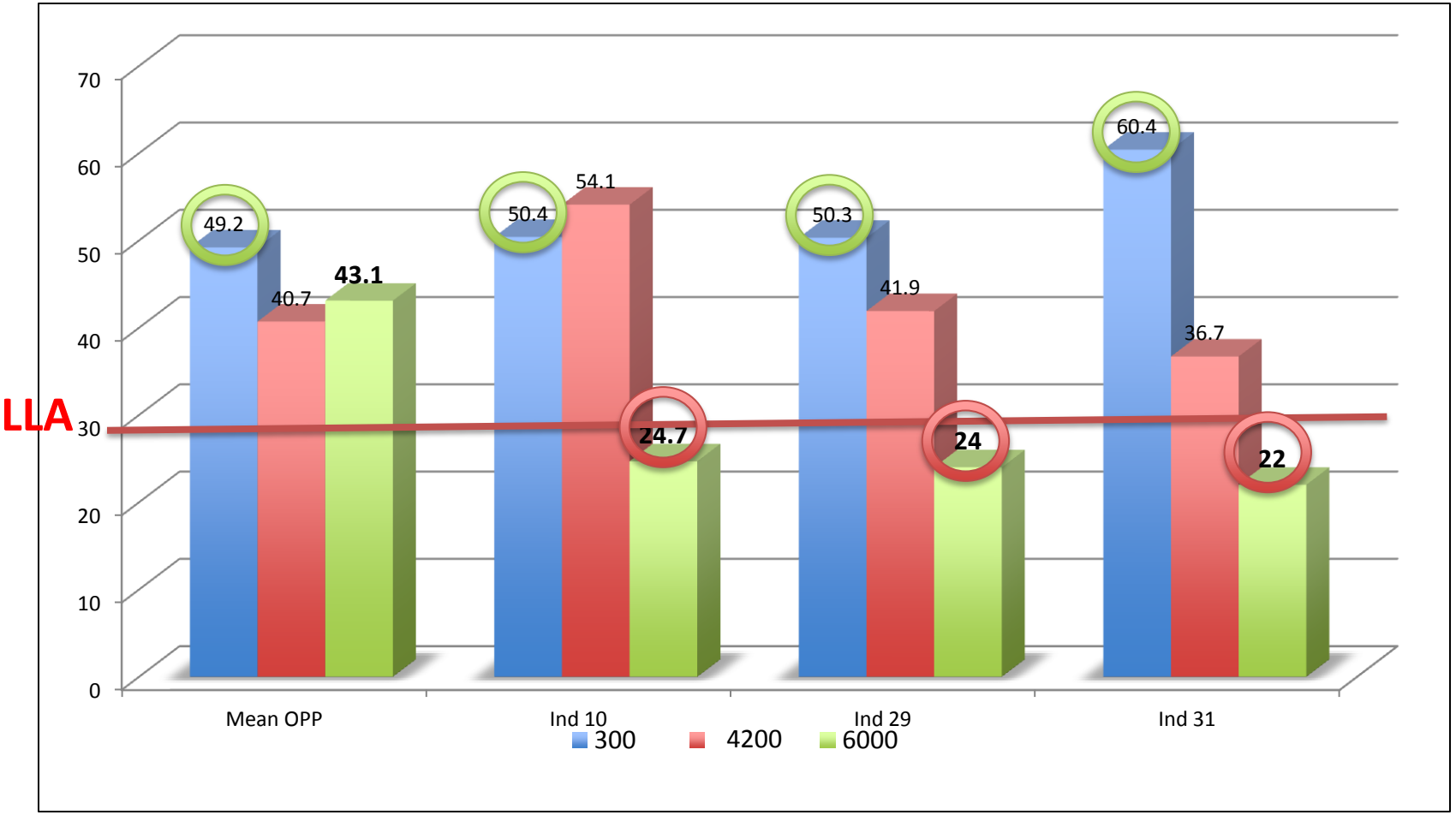
Lower Limit of Autoregulation LLA



Minderung des Blutflusses um 25% bis >30%

Very low OPP of selected subjects

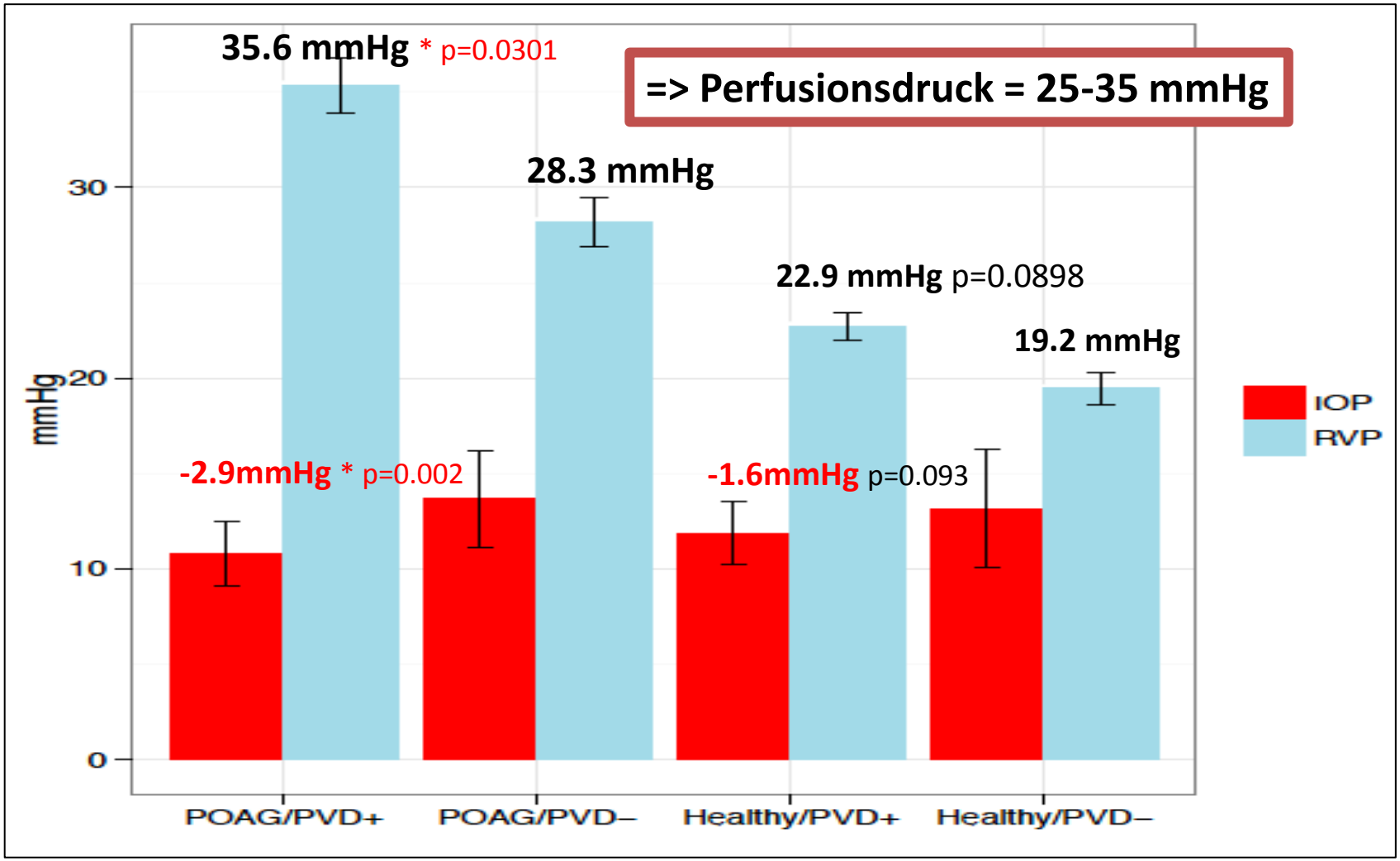
At or below Lower Limit of Blood Flow Autoregulation in Optic Nerve Head



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

Results POAG /FS

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



Fang, L., et al. (2014). "The effect of flammer-syndrome on retinal venous pressure." BMC Ophthalmol 14(1): 121ff.

Therapeutic suggestions 2013

Value of non-IOP lowering therapy for glaucoma:

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

Results Nifedipine 2015

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 **pati** **S** compared to patients lacking the FS (mean dec (CI): 5.2 to 9.3 vs. 12.3 t **ferences were accounted for in the IOP's** of the patie 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.

Evidence of Endothelin-1 (ET-1)

- **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 Hyopxia** (5).
- ET-1 acts as strong vasoconstrictor on vascular smooth vessels.

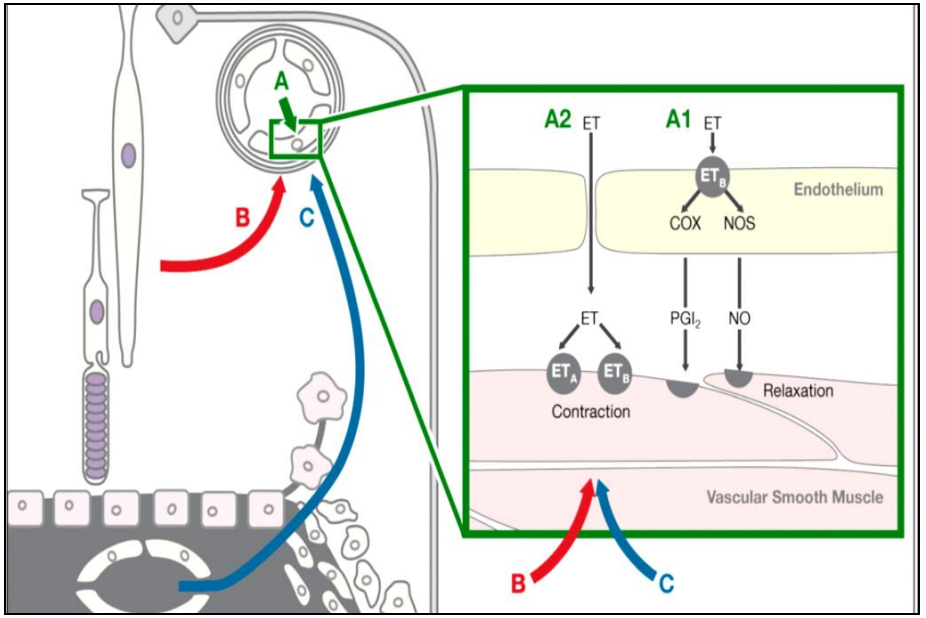
*(1) **Cellini, M. et al. 2012; Kaiser, H. et al. 1995***

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

(3) Iannaccone, A. et al. 1998

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

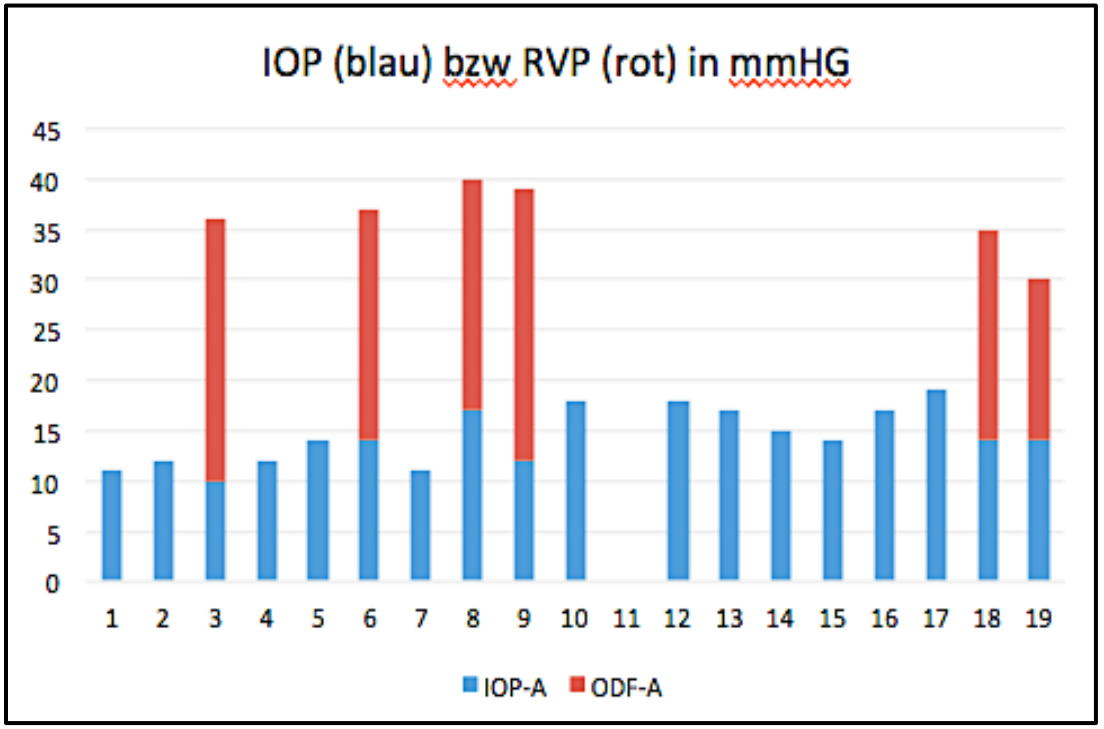
(5) Modesti, P. et al. 2006; Morganti, A. et al. 1995



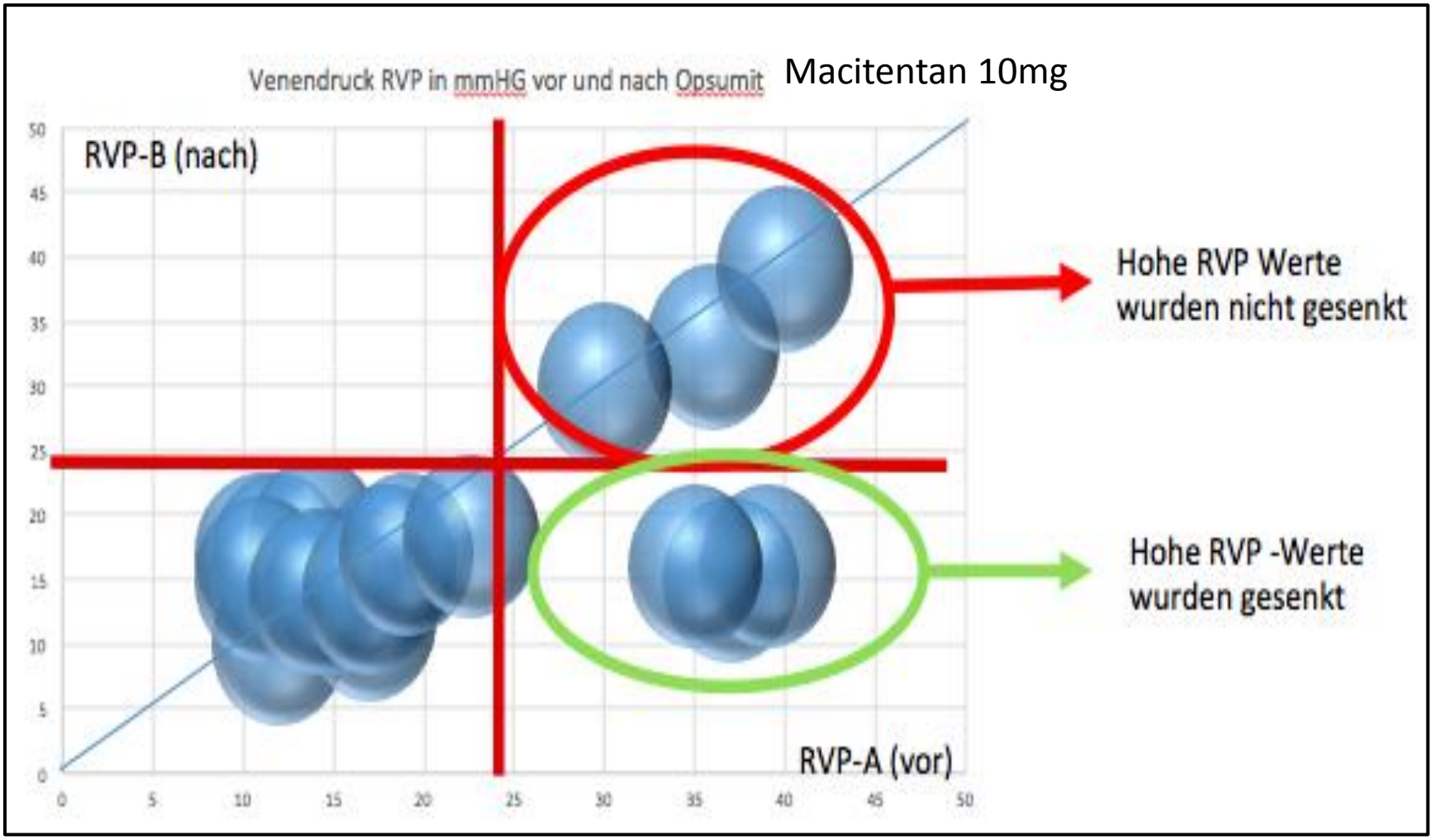
Results ET-1 Blocker "Diavolezza-Studie"

Diavolezza Studie durch das Universitätsklinikum Jena

(3'000 müM, Okt. 2014)



Results ET-1 Blocker "Diavolezza-Studie"



Results ET-1 Blocker “Diavolezza-Studie”

Retinal vessel regulation at high altitudes[1]

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.**

Conclusion

- 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)