

Glaukomforschung: Einfluss der Sauerstoffpenetration auf die Netzhaut

Tag der Optometrie, Mainz, 9. Okt.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



- Neue Sichtweise beim Glaukom wissen
- Kennenlernen der Kontaktglas-Dynamometrie
- Weitere kreislauforientierte okuläre Erkrankungen erfahren
- Zukunftsaussichten bei den optometrischen Untersuchungsmethoden erkennen

Einführung

The background of the slide is a solid blue color. In the lower half, there are several horizontal, wavy bands of slightly different shades of blue, creating a layered, water-like effect.

- Anamnese / Familien Hx
- Augeninnendruck mittels Tonometrie
- Hornhautdicke mittels Pachimetrie *
- Sehnervenkopf und Retinafasern Analyse mittels Biomikroskopie /
Ophthalmoskopie, HRT, GDx, OCT
- Ganglion Cell Complex (GCC) mittels Optical Coherence Tomography (OCT) *
- Vorderkammerwinkel und -strukturen mittels Biomikroskopie / Gonioskopie
- Funktionales Gesichtsfeld mittels Perimetrie
- Retinale Blutzirkulation mittels DVA, Oximetrie, Ophthalmo-Dynamometrie *

European Glaucoma Society, Terminology and Guidelines for Glaucoma, 2015
* Scientific research

Retinale Blutzirkulation

mittels Oximetrie,

Ophthalmodynamometrie *

** Scientific research*

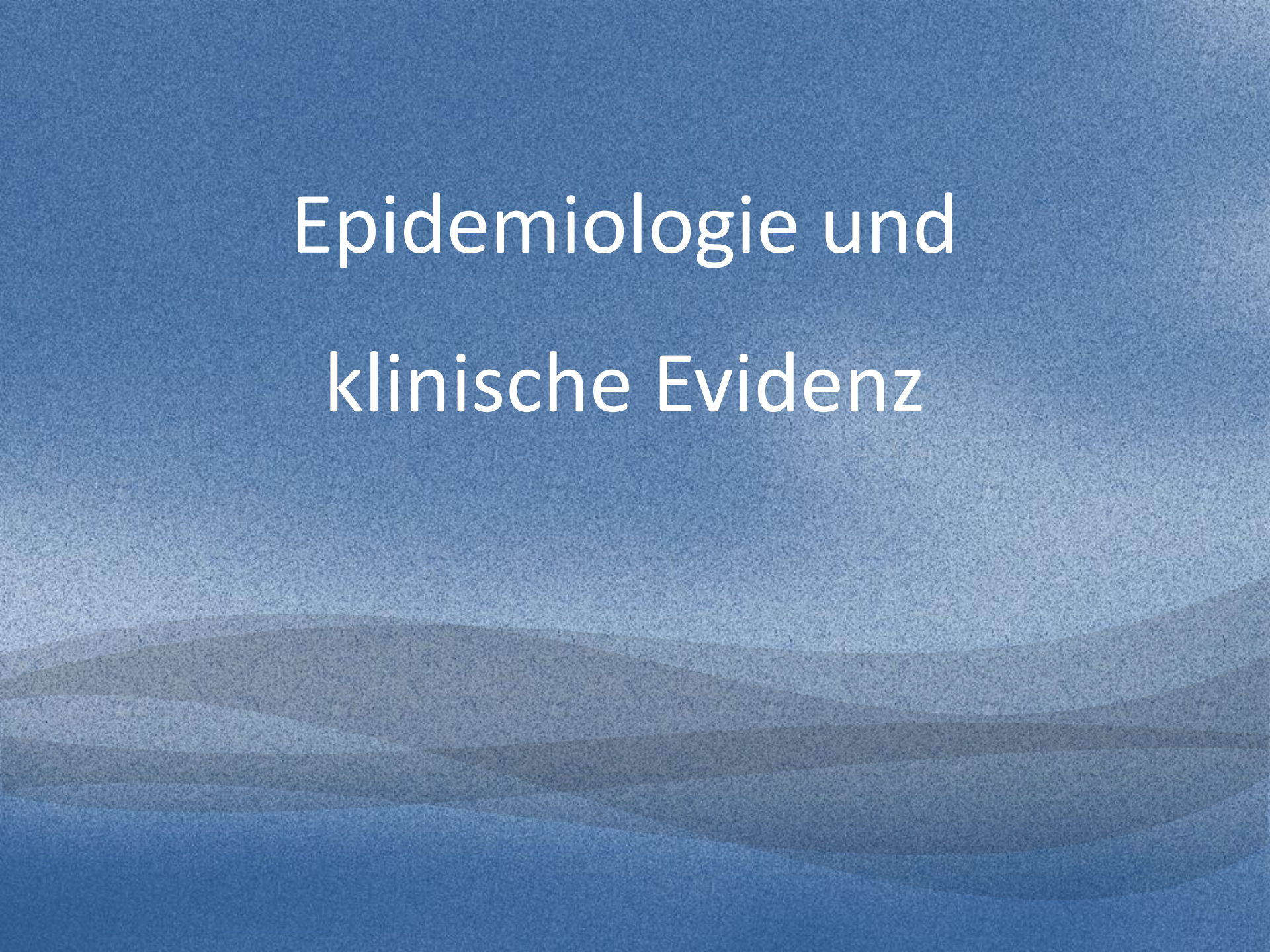


Klinisch akzeptiert ist, dass die okuläre Blutzirkulation:

1. ein Indikator für die systemische Blutzirkulation ist
2. relevant für die Pathogenese bei Glaukom und bei diabetischen Augenerkrankungen sei

Golzan, S.M. et al., Dynamic association between intraocular pressure and spontaneous pulsations of retinal veins. Curr Eye Res, 2011. 36(1): p. 53-9.

Epidemiologie und klinische Evidenz

The background of the slide is a solid blue color with a subtle, abstract pattern of wavy, horizontal lines in varying shades of blue and grey, creating a sense of depth and movement.

	<u>Patients</u>	<u>Prevalence</u>
1. Glaucoma	64.3 mio	3.54% (40-80yo)
2. Diabetes	387.0 mio	8.30% (all ages)
3. Vein Occlusion	16.4 mio	0.52% (20yo+)
		<u>Incidence</u>
4. High Altitude Sickness	n.A.	42% (3000m/9'842ft)
Summit/Death ratio (8000m+) 847		1.5% - 38% !

References:

1. Tham, et al., *Global Prevalence of Glaucoma and projections of Glaucoma burden through 2040: a systematic review and meta-analysis*. *Ophthalmology*, 2014 Nov;121(11):2081-90
 2. International Diabetes Federation, *Diabetes Atlas: Sixth Edition; 2014 update*
 3. Rogers et al., *The Prevalence of Retinal Vein Occlusion: pooled data from populations studies from US, EU, Asia and Australia*. *Ophthalmology*, 2010 Feb;117(2):313-19
 4. Hackett and Roach, *High Altitude Illness*. *N Engl J Med*, 2001 July; 345(2):107-114
- Eberhard Jurgalsky for 8000ers.com, 2008

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

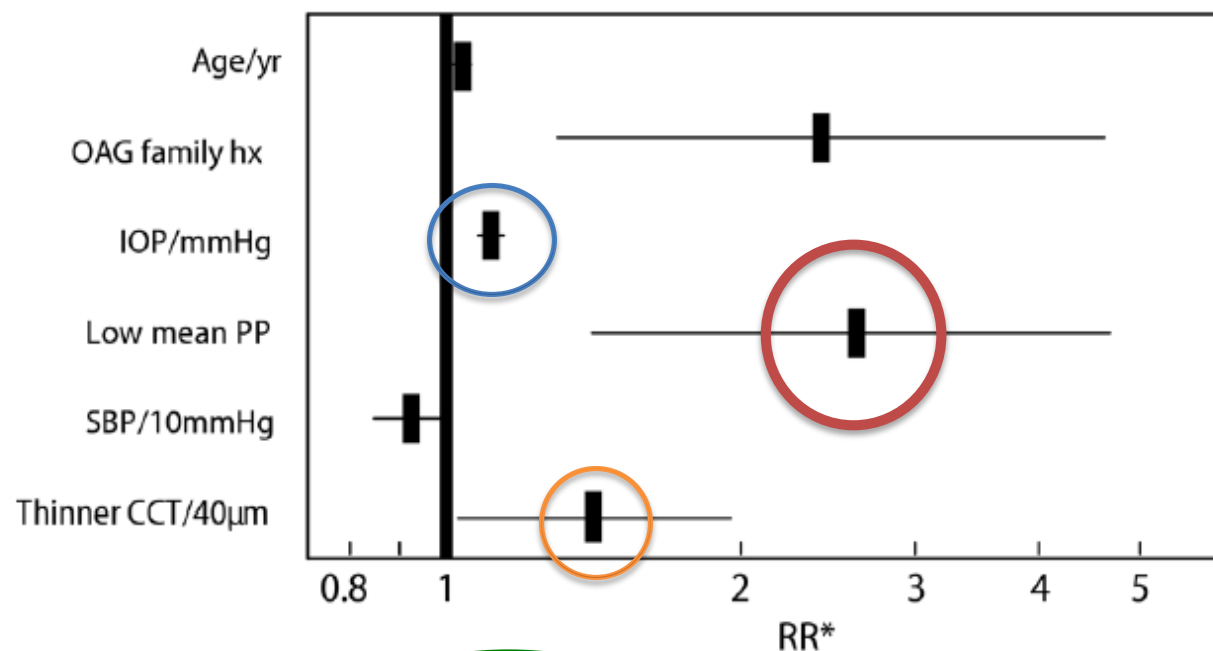


Figure 1. Risk factors for definite open-angle glaucoma (OAG; n = 3222). hx = history; PP = perfusion pressure; RR = risk ratio; SBP = systolic blood pressure. *Based on Cox regression models, adjusting for age, gender, intraocular pressure (IOP), and IOP- and blood pressure-lowering treatment; central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

Erhöhter retinaler Venendruck ist publiziert bei:

- Glaukom (*Fang, Baertschi et al. 2014; Pillunat et al. 2014; Morgan et al. 2009; Jonas, Harder 2003*)
- Venenverschluss (*Mozaffarieh, Baertschi et al. 2014; Yasuda et al. 2010; Jonas et al. 2007*)
- Flammer Syndrom (*Fang, Baertschi et al. 2014*)
- Diabetes (*Cybulska, Baertschi et al. 2015*)
- Hypoxie - Höheninduziert (*Baertschi et al. 2016*)
 - Höheninduzierte temporäre Amaurosis (*Baertschi, ISMM 2014*)
 - Retina Blutungen und Sehnervenkopfödem (*multiple 1975-2009*)

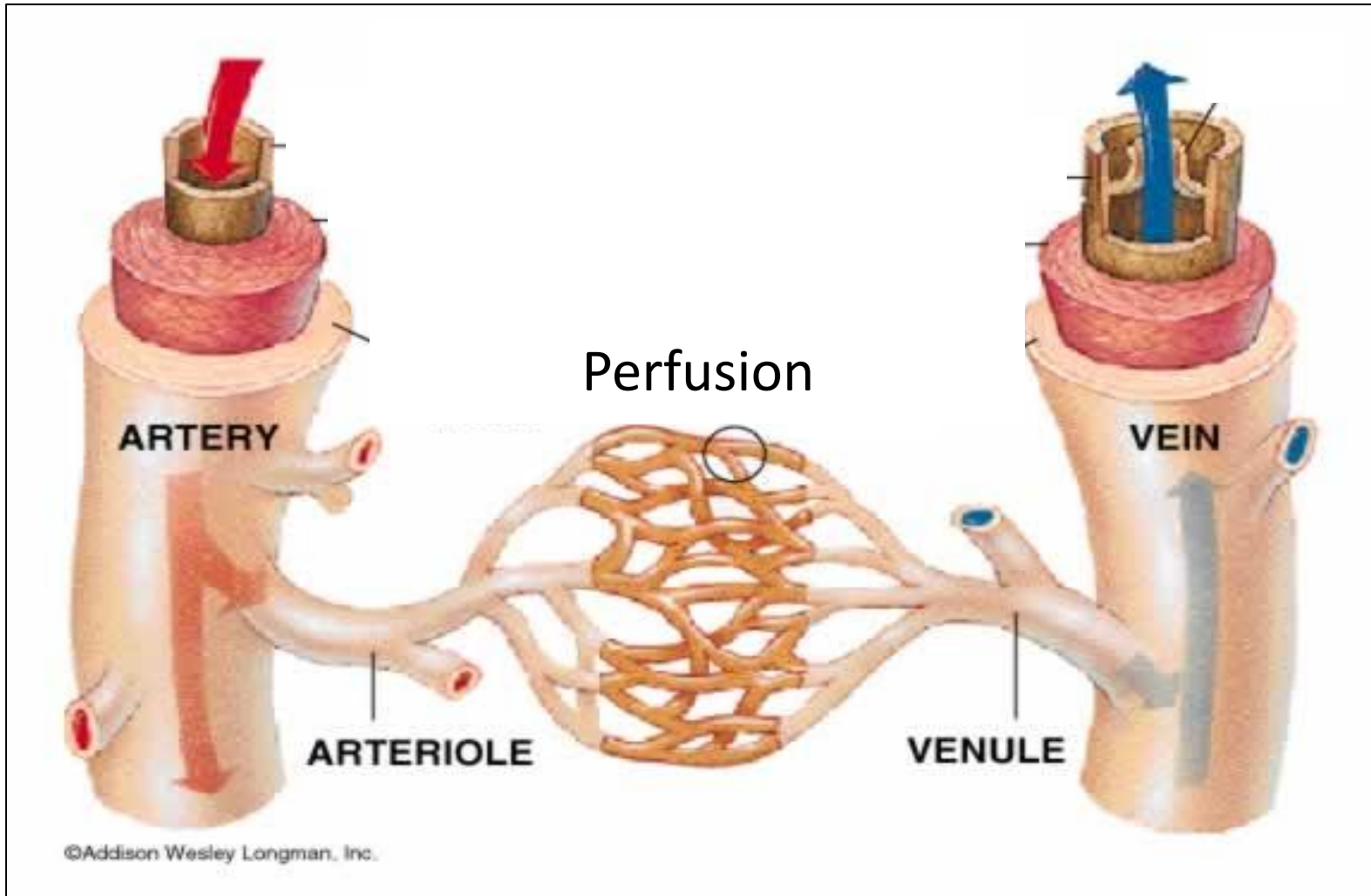
Definition und Methode

- Rolle des Perfusiondruckes ?
- Rolle der venösen Pulsation ?
- Rolle von Endothelin-1 auf den retinalen Venendruck ?
- Was ist ein Ophthalmo-Dynamometer ?

“Perfusionsruck 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.





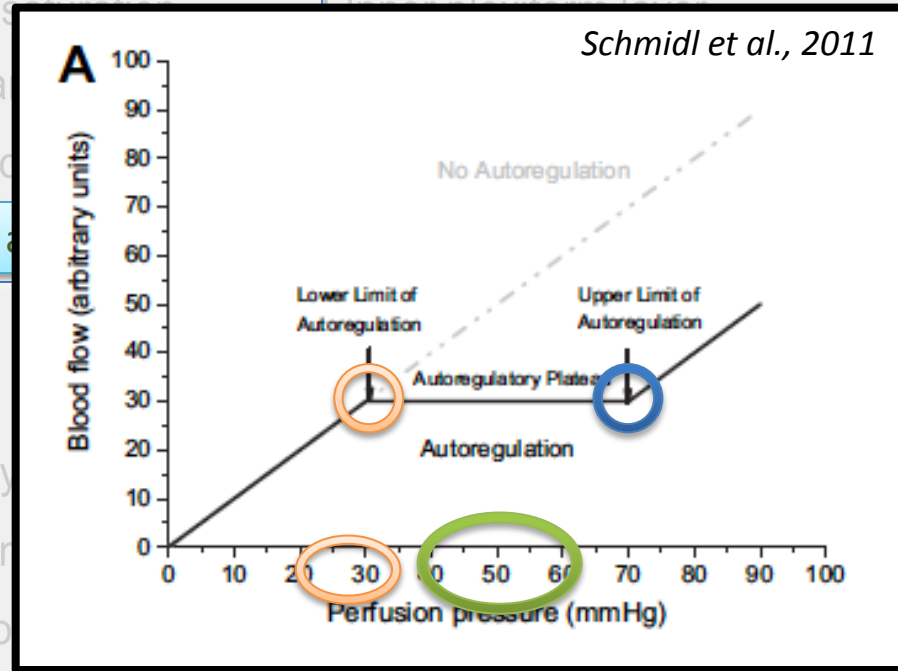
Interconnection between Arteries, Arterioles, Capillaries and Venules
(Reproduction with Permission of Pearson Education)

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

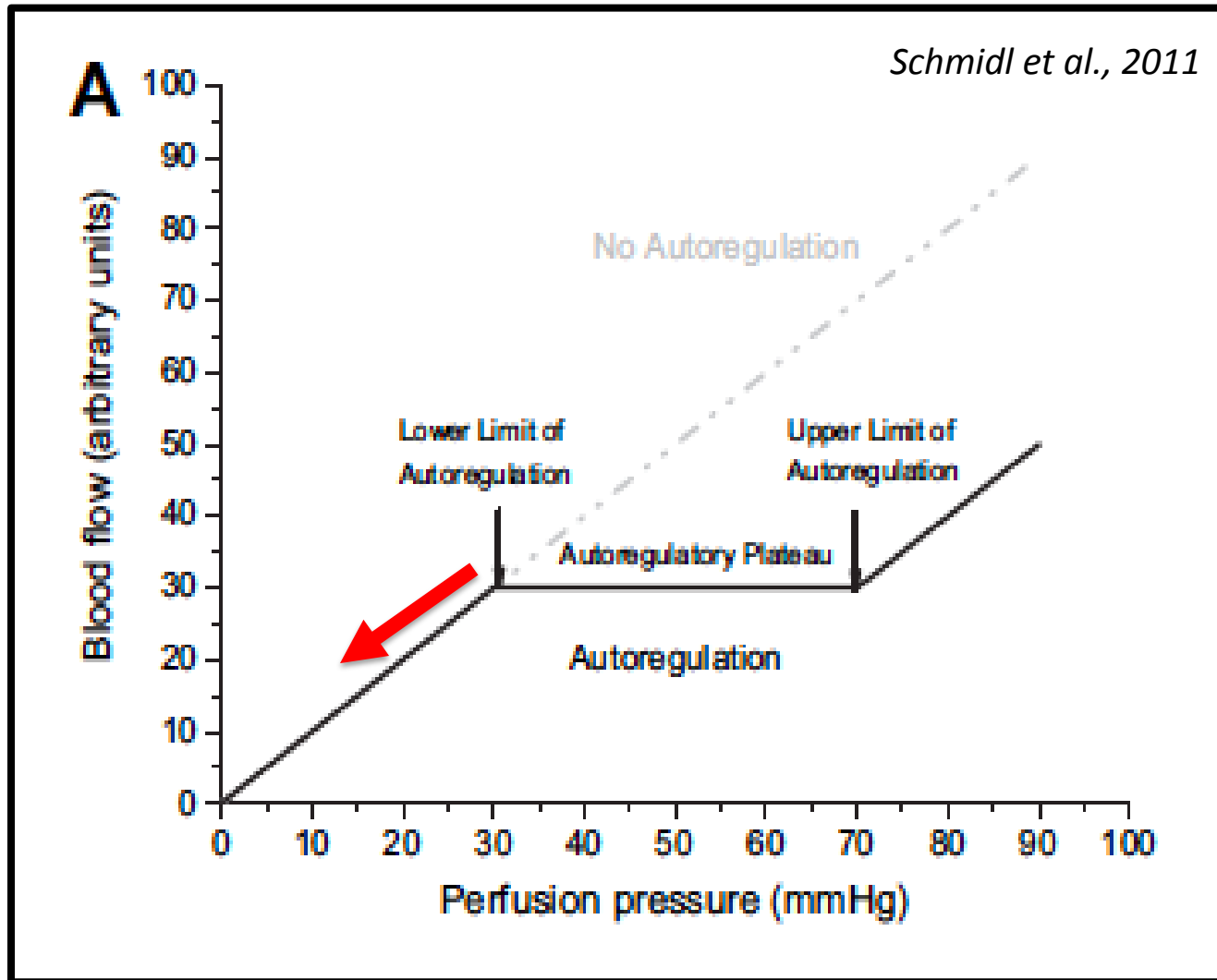
- “Ungenügende okuläre Perfusion der Netzhaut verursacht eine Mangeldurchblutung und führt zu einem Sauerstoffmangel im Gewebe, welches wiederum schädliche, das Sehen bedrohende Effekte auslöst.”

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.

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

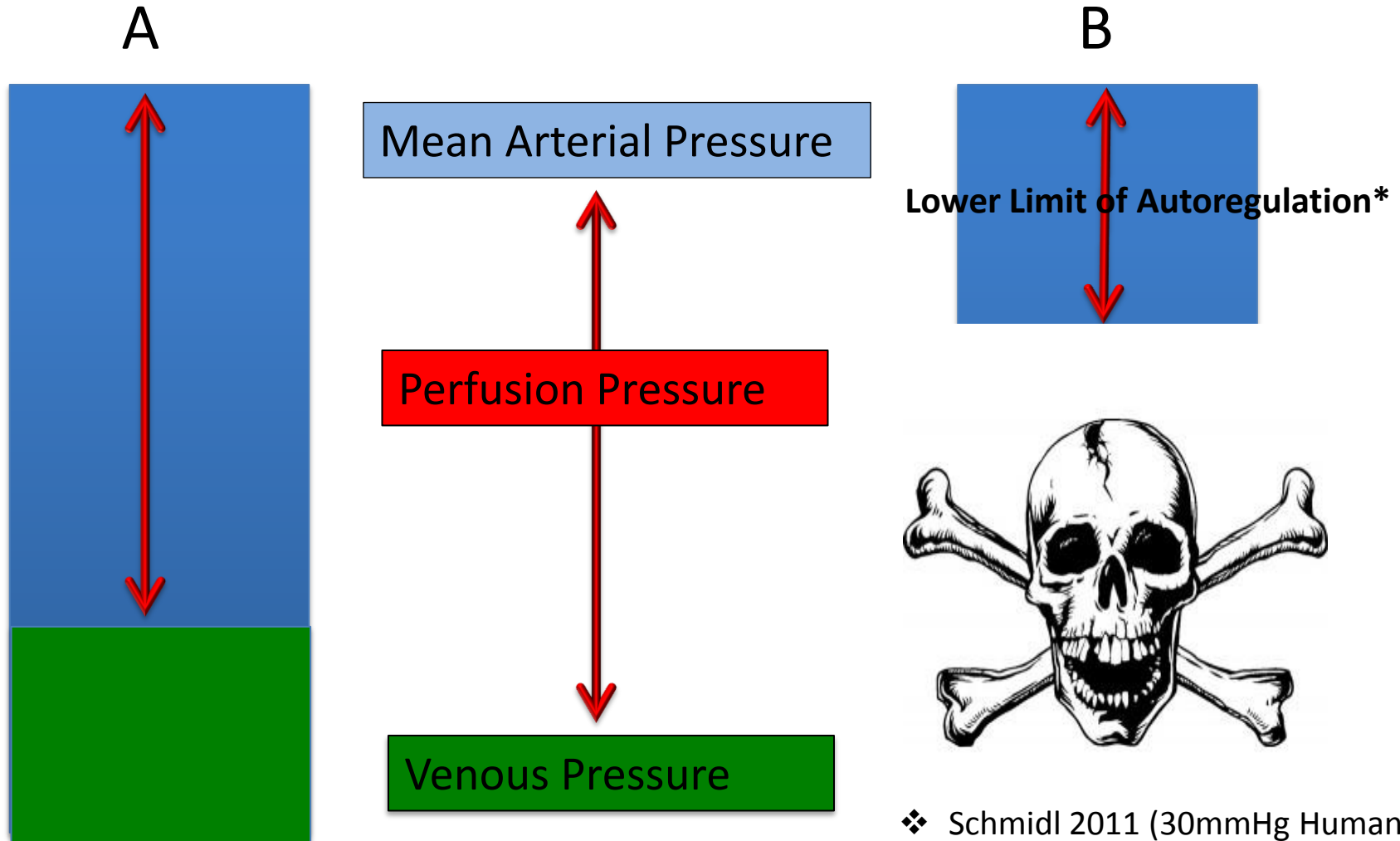


- Riva, C.E., et al., *Autoregulation of human optic nerve head blood flow in response to acute changes in ocular perfusion pressure*. Graefes Arch Clin Exp Ophthalmol, 1997. **235**(10): p. 618-26.
- Riva, C.E., S.D. Cranstoun, and B.L. Petrig, *Effect of decreased ocular perfusion pressure on blood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



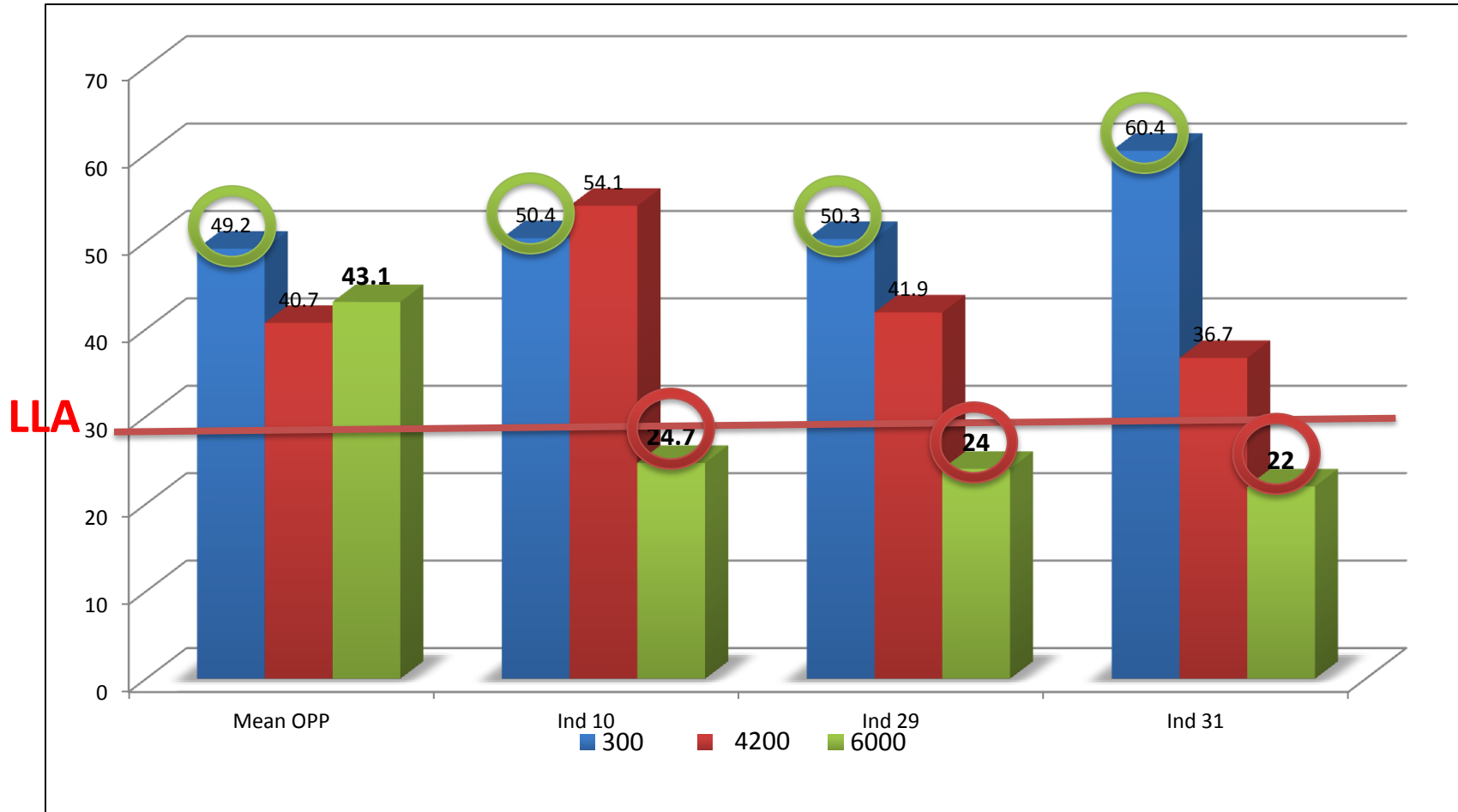
**Minderung des Blutflusses am Sehnervenkopf bei Glaukom
um rund 20% (Dr. med. Claudia Lommatzsch, DOG 2016)**

venösen Blutdrucks zum Perfusionsdruck



- ❖ Schmidl 2011 (30mmHg Humans)
- ❖ Riva 1997 (22mmHg Humans)

Tiefer als das "Lower Limit of Blood Flow Autoregulation" am Sehnervenkopf



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

Spontaner retinaler Venenpuls (SVP) erscheint, wenn der umgebende Augeninnendruck IOP identisch dem Venendruck ist.



Prevalenz des SVP ? (% gesunder Px)

99 %

66 %

33 %

PHYSIK !

“Wenn wir akzeptieren, dass der Perfusionsdruck ein wichtiger Aspekt des Sehnervenschadens beim Glaukom darstellt, dann benötigen wir reale Messungen des Augen- und Sehnervenkopf Perfusionsdruckes.”

Joseph Caprioli, MD

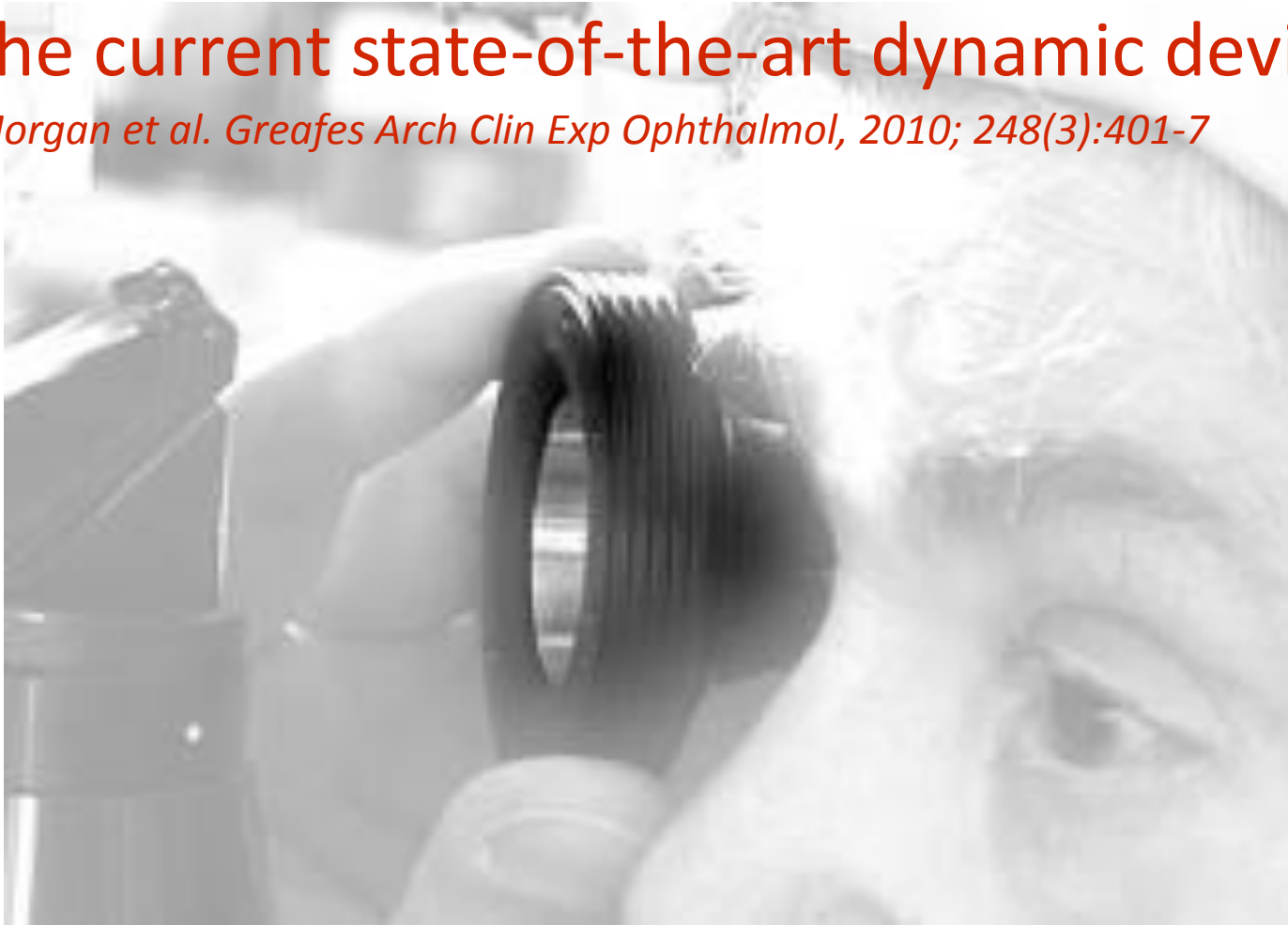
interviewed by Tony Realin, MD and William Trattler, MD

for EyeWorld Online, July 2008

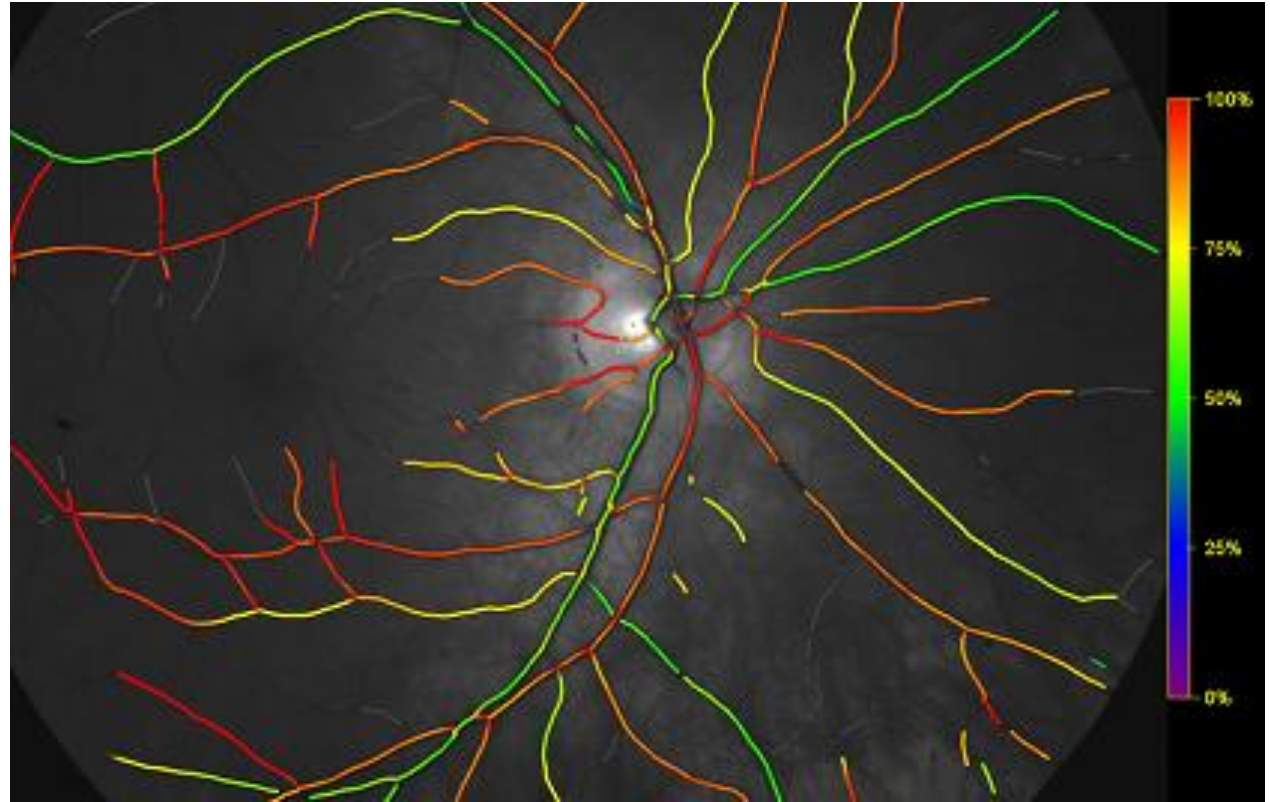


“The current state-of-the-art dynamic device, ... “

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

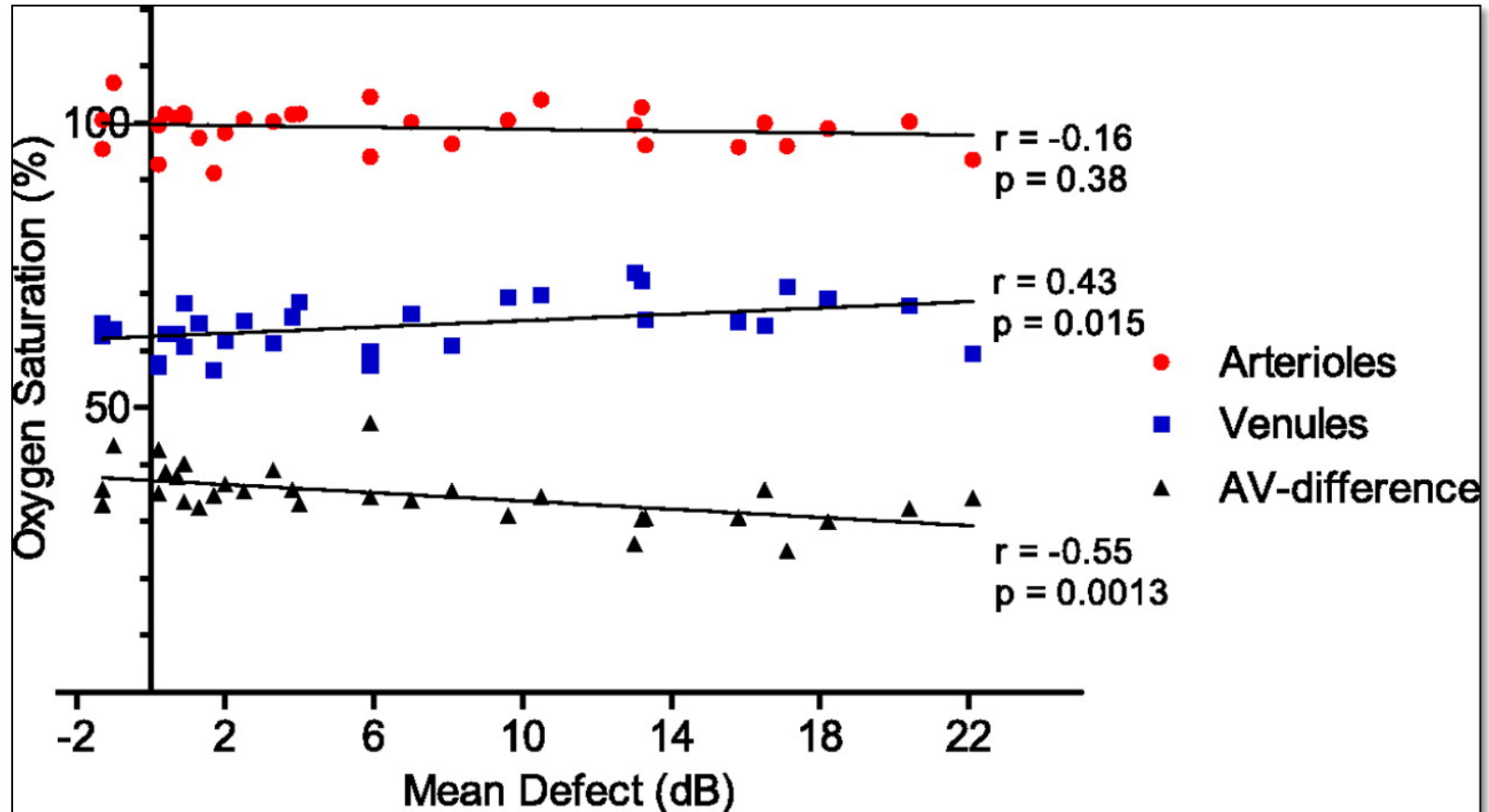


Ophthalmo-Dynamometry nach Dr. Bernhard Loew, Deutschland



Retinal Oximetry T1 nach Prof. Einar Stefansson, Island

Blut- und Perfusionsdruck bei zunehmendem Gesichtsfeldschaden



Olafsdottir, O. B., et al. (2011). "Retinal oximetry in primary open-angle glaucoma." Invest Ophthalmol Vis Sci **52**(9): 6409-6413.

Hypothesen und Resultate

Descriptive, Exploratory or Experimental Designs,
Clinical Series or Clinical Trials,
Case Control or Cross Sectional Studies,
Prospective Cohort Studies

Studie 1: Venendruck im nicht betroffenenene Auge von Px mit retinalem Venenverschluss

Ziel: Ermitteln des RVP im betroffenen und dem nicht-betroffenen Auge von Px mit unilateralem retinalen Venenverschluss, verglichen mit einer gesunden Kontrollgruppe.

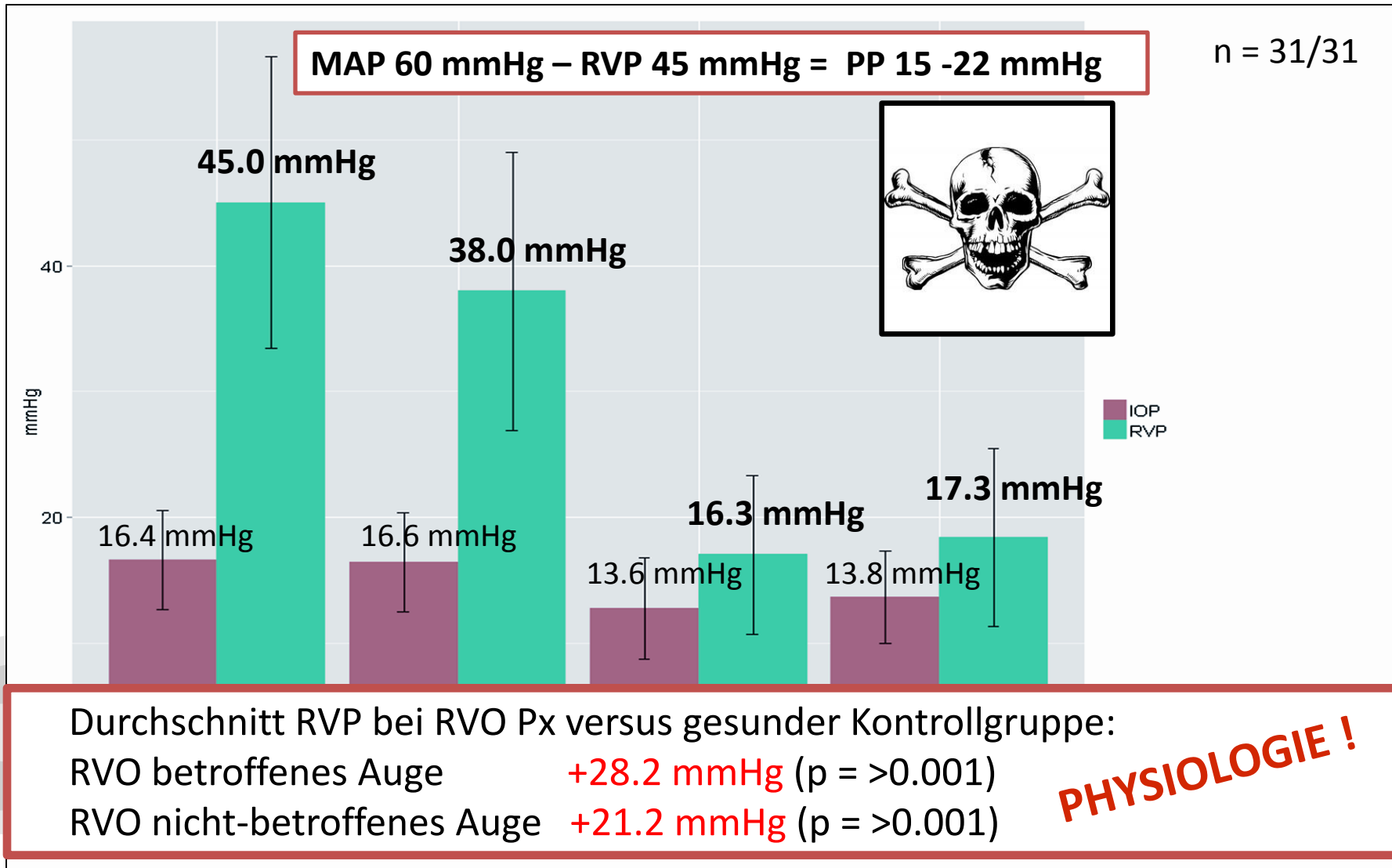
Method: Exploratory, case control study

Statistics: Descriptive, ANOVA, linear mixed model

Population: 31 RVO Px, 31 controls, University Hospital Basel

Gender: RVO 15 women / 16 men
controls 14 women / 17 men

Mean age: 62.8 yo RVO / 62.6 yo controls



Diskussion and Konklusion Studie 1

- Der retinale Venendruck ist signifikant erhöht im betroffenen und dem nicht-betroffenen Auge bei retinalem Venenverschluss Patienten verglichen mit der gesunden Kontrollgruppe. Possible Explanations:
- The underlying eye disease affects both eyes but becomes clinically manifest only in the more severe affected eye.

or

- RVP is increased due to systemic factors such as increased ET-1.
- Further studies are needed to clarify this.

Studie 2: Der Effekt des Flammer Syndroms auf den retinalen Venendruck in Glaukom Patienten und Gesunden

Ziel: Ermitteln des RVP in Glaucoma Patienten und bei einer gesunden Kontrollgruppe mit und ohne Flammer Syndrome.

Method: Exploratory, cross sectional study

Statistics: Descriptive, ANOVA, linear mixed model

Population: 30 POAG Px, 30 controls, University Hospital Basel

Gender: POAG FS+ 8 w / 7 m ; FS- 7 w / 8 m

Controls FS+ 7 w / 7 m ; FS- 10 w / 6 m

Mean age: POAG FS+ 67.0 yo / FS- 62.8yo

Controls FS+ 60.4 yo / FS- 56.6yo

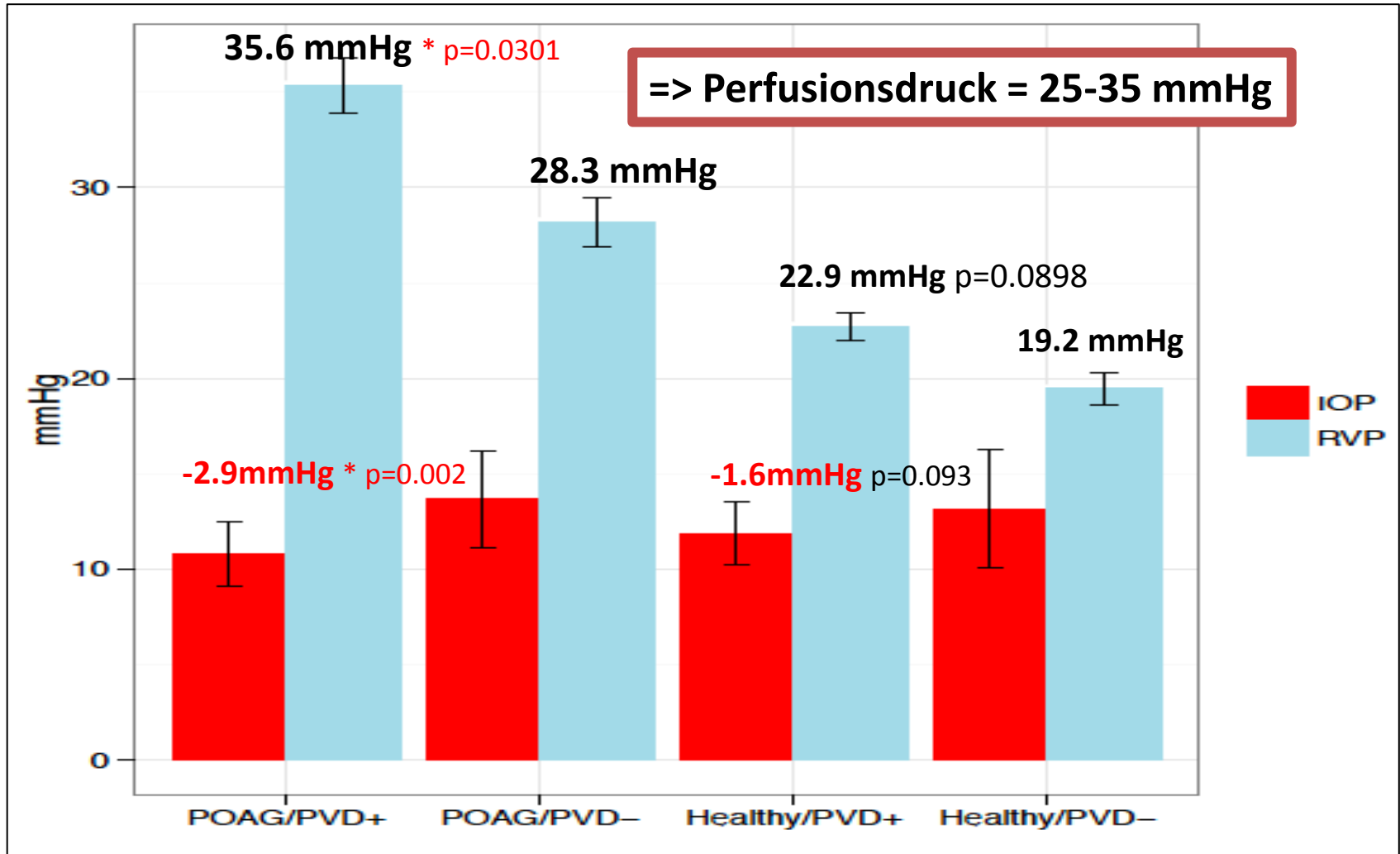
Typische Anzeichen und Symptome:

- Kalte Hände und Füße
- Tiefer Blutdruck
- Schlanke Figur
- Einschlafprobleme
- Geringes Durstempfinden
- Medikamentenempfindlichkeit
- (Kopfschmerzen / Migräne)



By courtesy of Prof. Stodtmeister and Mrs. Krstic

IOP und RVP bei POAG FS+/FS- und Gesunden FS+/FS- (n=30/30)



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

Diskussion und Konklusion Studie 2

- Patienten mit Flammer Syndrome (POAG und Gesunde) weisen einen signifikant höheren RVP auf. ($p=0.0103$)
- Patienten mit FS hatten signifikant tieferen IOP. ($p=0.02$) Healthy subjects with FS had a tendency to lower IOP.
- Reduzierter und instabiler Perfusionsdruck wurde als Risikofaktor bei der Glaukomprogression beschrieben. (Pilunat 2014, Choi 2013, Leske 2011, Ramdas 2011, Bonomi 2000)
- Reason for increased RVP: structural changes of the ONH and/or local dysregulation of retinal veins due to increased ET-1 in POAG. (Cellini 2012, Lee 2012, Kaiser 1995)
- Causal relationship of increased RVP or decreased IOP in FS needs to be further evaluated.

Klinische Therapieansätze durch den Ophthalmologen

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

RELATED 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 treatment has been conducted on treatment, we can still assist these patients based on lifestyle management.

Lifestyle management
Most subjects...

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

... recommend eating enough to avoid... blood pressure is low, salt and fluid intake can be... to avoid excessive nocturnal blood pressure dips. Omega-3 fatty acids, as... 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.



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. Turttschi, 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 of 12.5 mmHg vs. 12.3 mmHg, $P < 0.001$). **Differences were accounted for in the IOP's** of the patient 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 Hypoxia** ⁽⁵⁾.
- ET-1 acts as strong vasoconstrictor on vascular smooth vessels.

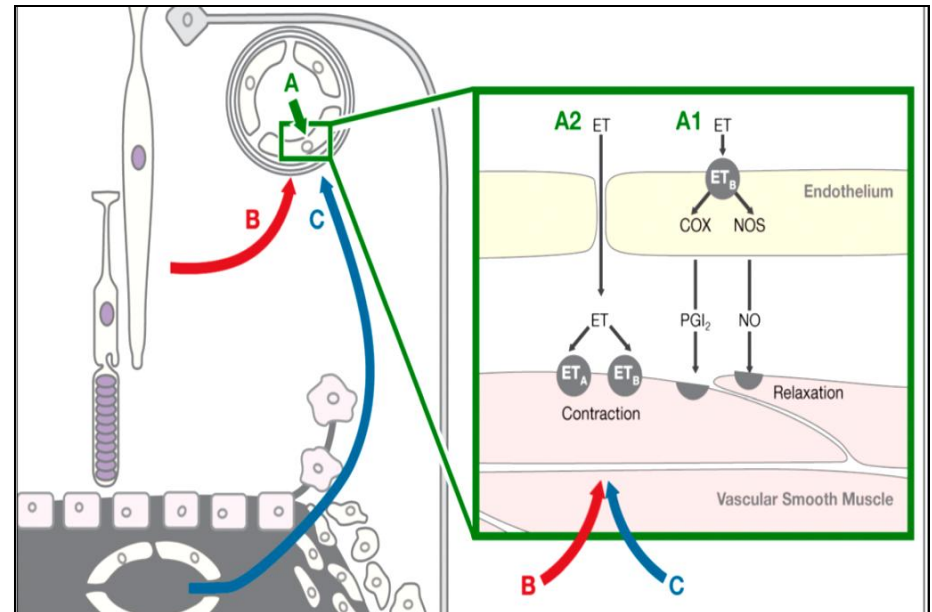
(1) Cellini, M. et al. 2012; Kaiser, H. et al. 1995

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

(3) Iannaccone, A. et al. 1998

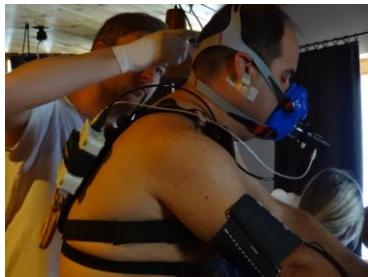
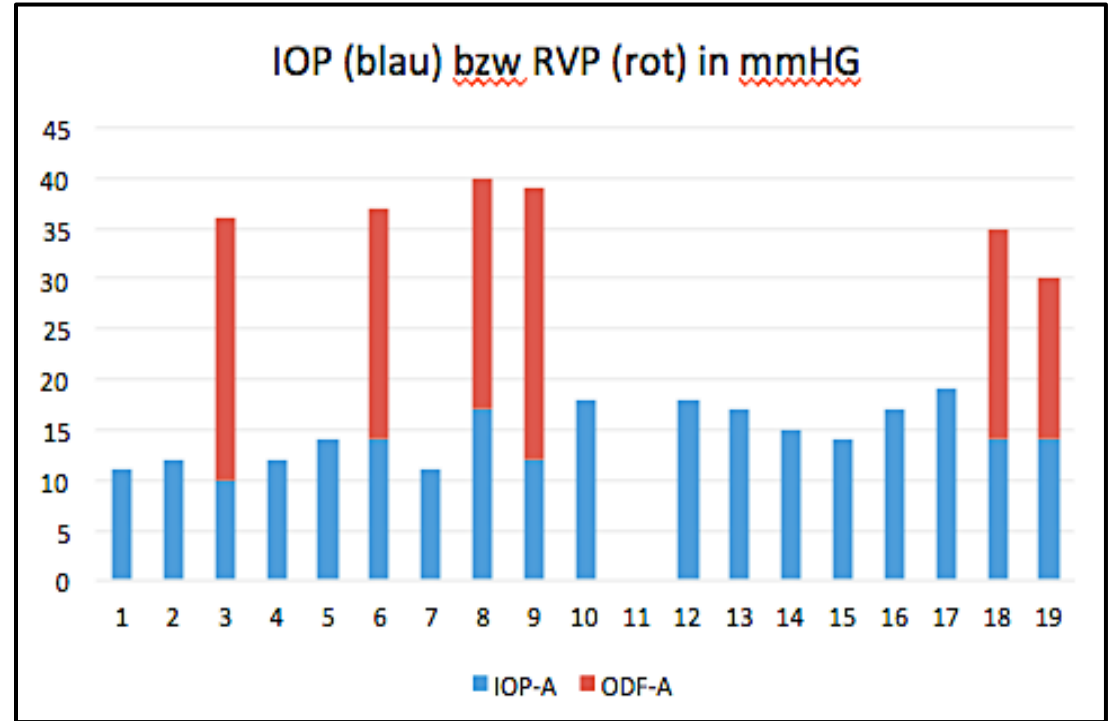
(4) Flammer, J. et al. 2013,

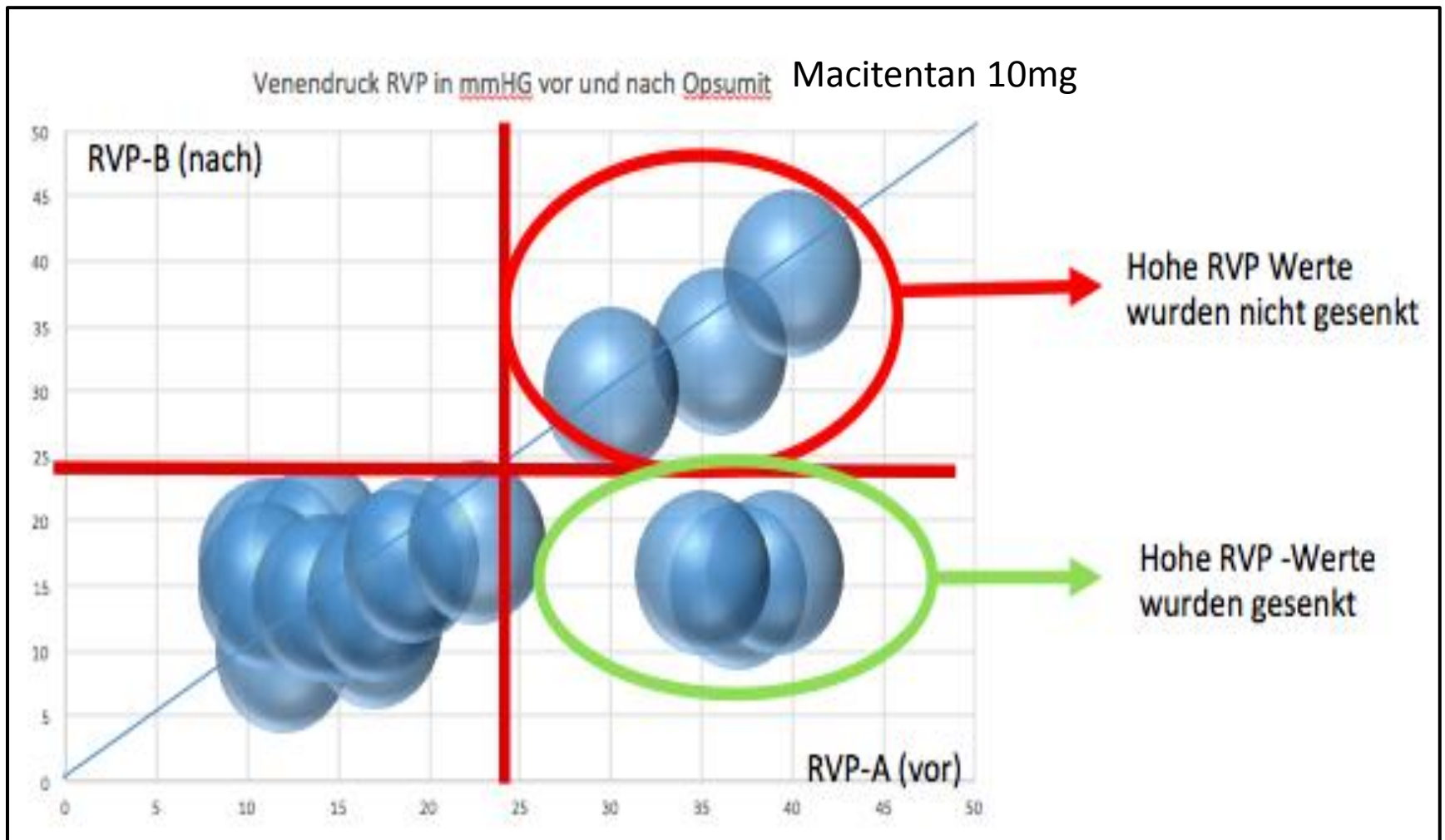
(5) Modesti, P. et al. 2006; Morganti, A. et al. 1995



Diavolezza Studie durch das Universitätsklinikum Jena

(3'000 müM, Okt. 2014)





Retinal vessel regulation at high altitudes¹

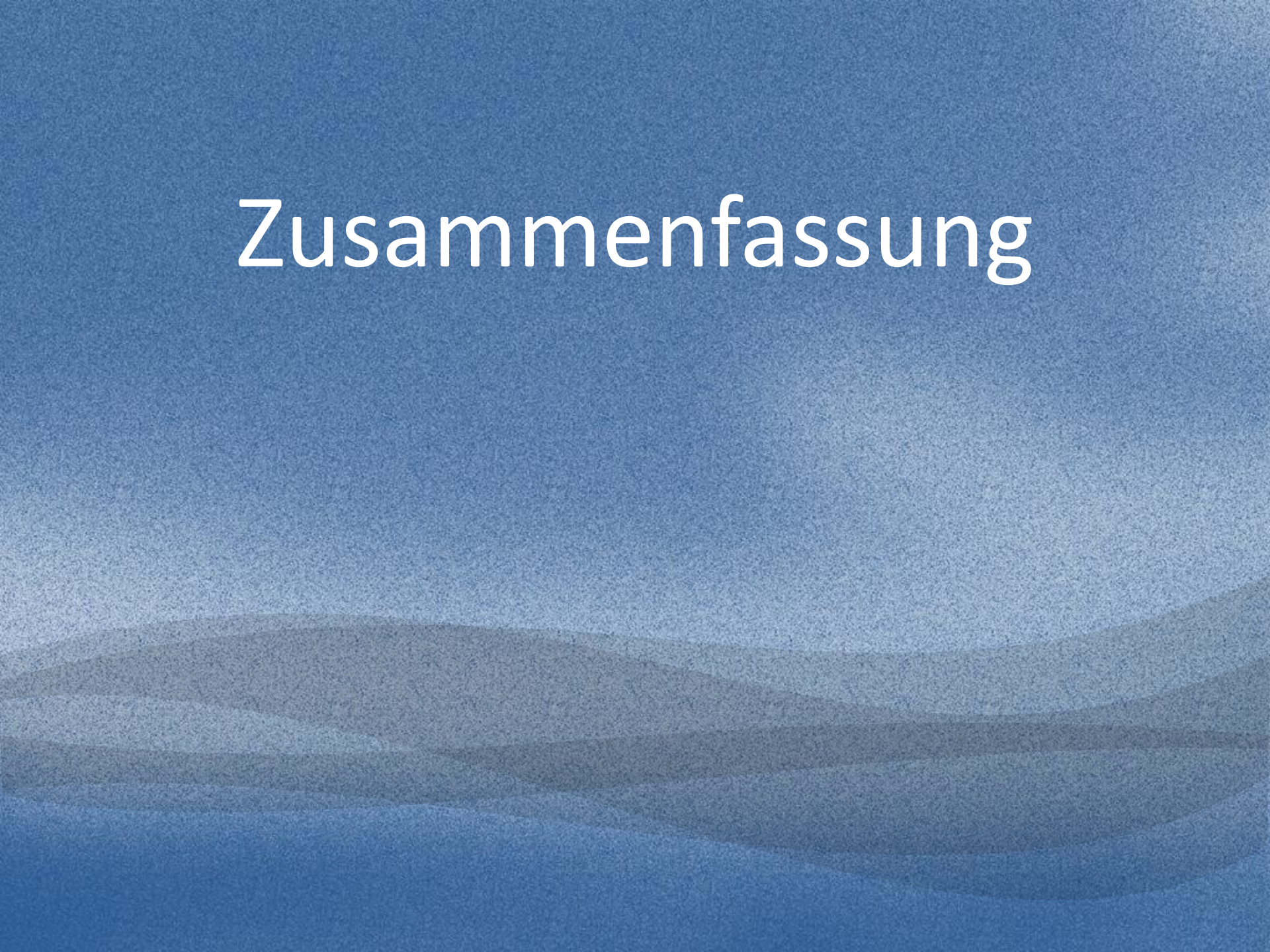
Article type: Research Article

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.**

Zusammenfassung

The background of the slide is a solid blue color. In the lower half, there are several horizontal, wavy lines in a slightly darker shade of blue, creating a layered, landscape-like effect.

1. Retinal venous pressure (RVP) ist ein essentieller Faktor um den retinalen Perfusionsdruck zu ermitteln.
2. RVP kann präzise, reproduzierbar, schnell und günstig mittels Ophthalmo-Dynamometrie ermittelt werden.
3. RVP ist erhöht bei okulären Erkrankungen wie Glaukom, diabetischer Retinopathie und retinalem Venenverschluss.
4. RVP ist erhöht bei Flammer-Syndrom und chronischem Sauerstoffmangel.

Ja, es gibt **klinische Behandlungsanwendungen** bei erhöhtem retinalem Venendruck (RVP) durch den Augenarzt:

- 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 (Diavolezza-Studie publiziert 2016)*

- Retinaler Venen- und okulärer Perfusionsdruck sind evident.
- Ist kein spontaner Venenpuls sichtbar, so ist RVP höher als IOP und muss für das komplette klinische Bild gemessen werden.
- Hoher Venendruck hat einen Einfluss auf den Sauerstoffmangel und die Ernährung der Retina. Vice-Versa !
- Achten Sie ab heute auf das Vorhandensein eines Venenpulses.
- Zu hoher Venendruck (zu tiefer Perfusionsdruck) sollte therapiert werden. Sprechen Sie mit Ihrem lokalem Augenarzt darüber.

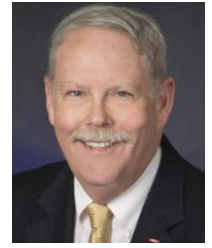
Mentors Thesis:

- **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)



*Beispiel Venenpulsation aus dem Probandengut der Diavolezza Studie 2014.
Aufgenommen mit dem DVA.*