

# Retinaler Venendruck bei Glaukom, Diabetes mellitus, Venenverschluss und bei Flammer Syndrom

Dr. Michael Bärtschi

Ph.D. in Biomedicine, etc  
eyeness AG, Bern

UMBRIA Club, September 2015

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

Since June 2011, Prof. Josef Flammer and myself are 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



# !! Brain Storming !!



The diagram on the left shows a 'System Tonometry' setup. It includes a 'Contactable Dynamometer' connected to a 'Sensor' and a 'Data Acquisition System' (represented by a laptop). The setup is used to measure 'VPP' (Venous Pulsation Pressure).

The diagram on the right is a schematic of an 'Endothelial Cell'. It shows 'Hem. vein control' and 'Hem. vein' on the left. The cell is influenced by 'Shearing', 'Rolling', 'ET-1', 'Hormones', 'Mediators', and 'O<sub>2</sub>'. The cell's response is 'VSMC' (Vascular Smooth Muscle Cell), which can lead to 'Dilation' or 'Constriction'.

**Goals:**

- precise
- reproducible
- easy to use
- observer controlled
- multi use (observation & documentation)
- portable (compression chamber & outdoor)
- System 'Tonometrie'

**VPP = IOP + 0.72 • ODF**

Central vein pressure ↑

- Glaucoma
- cerebrospinal fluid pressure
- increased Excitation
- ↑ systemic blood pressure
- ↓ pulse blood pressure
- ↑ venous resistance
- ↓ retinal microvascular resistance

Risks for RVO

- Mechanical compr./Thrombotic occl.
- Glaucoma
- ↑ IOP
- Vasoconstriction / hypoxic tissue

Abbreviations:

ODF	ophthalmo-dynamometric - force
PVD	primary vascular dysregulation
SVD	secondary
VPP	venous pulsation pressure
OPT	ocular pressure tonometrie
VEGF	vascular endothelial growing factor
VSMC	vascular smooth muscle cells
RVA	retinal vessel analyzer
ORA	ocular response analyzer




# Introduction

Known and accepted is that ocular circulation:

1. is an indicator for systemic circulation
2. has been suggested to be relevant in the pathogenesis  
of glaucoma and diabetic ocular disease


*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.*



## Role of Ocular Perfusion Pressure OPP

- “Inadequate ocular perfusion of the retina can cause ischemia leading to decreased oxygen supply (hypoxia) in tissues, which may result in deleterious sight-threatening effects.”

*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.*





# Epidemiological and Clinical Evidence



	<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



## Altered Retinal Venous Pressure is published for:

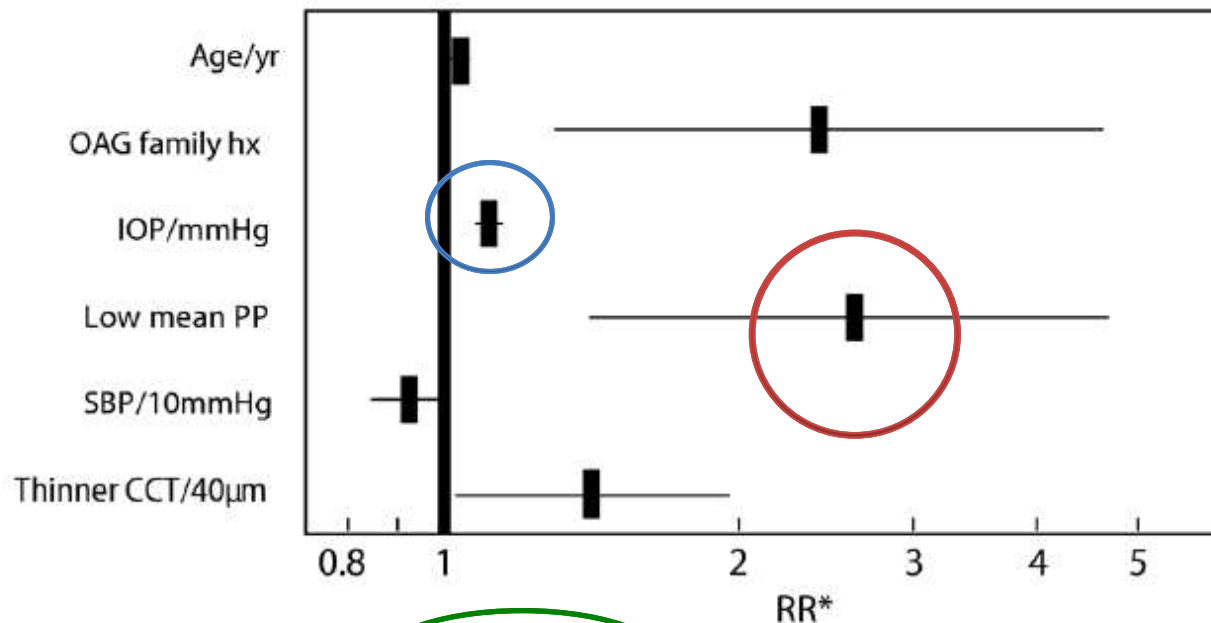
- Glaucoma *(Pillunat 2014, Mozzafarieh et al. 2014, Morgan 2009, Jonas 2003)*
- Vein occlusion *(Mozzafarie et al. 2014, Yasuda 2010, Jonas 2007)*
- Flammer Syndrome *(Mozzafarie et al. 2014)*
- Diabetes *(Cybulska et al. 2015)*
- High Altitude:
  - retinal Hemorrhages and
  - Optic Nerve Head Edema *(multiple 1975-2009)*
  - potentially in temporary Amaurosis *(Bärtschi, ISMM 2014)*

# Risk Factors for Incident Open-angle Glaucoma

*The Barbados Eye Studies* 2008


M. Cristina Leske, MD, MPH,<sup>1,2</sup> Suh-Yuh Wu, MA,<sup>1,2</sup> Anselm Hennis, FRCP(UK), PhD,<sup>1,3,4</sup>  
Robert Honkanen, MD,<sup>2</sup> Barbara Nemesure, PhD,<sup>1,2</sup> BESs Study Group

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

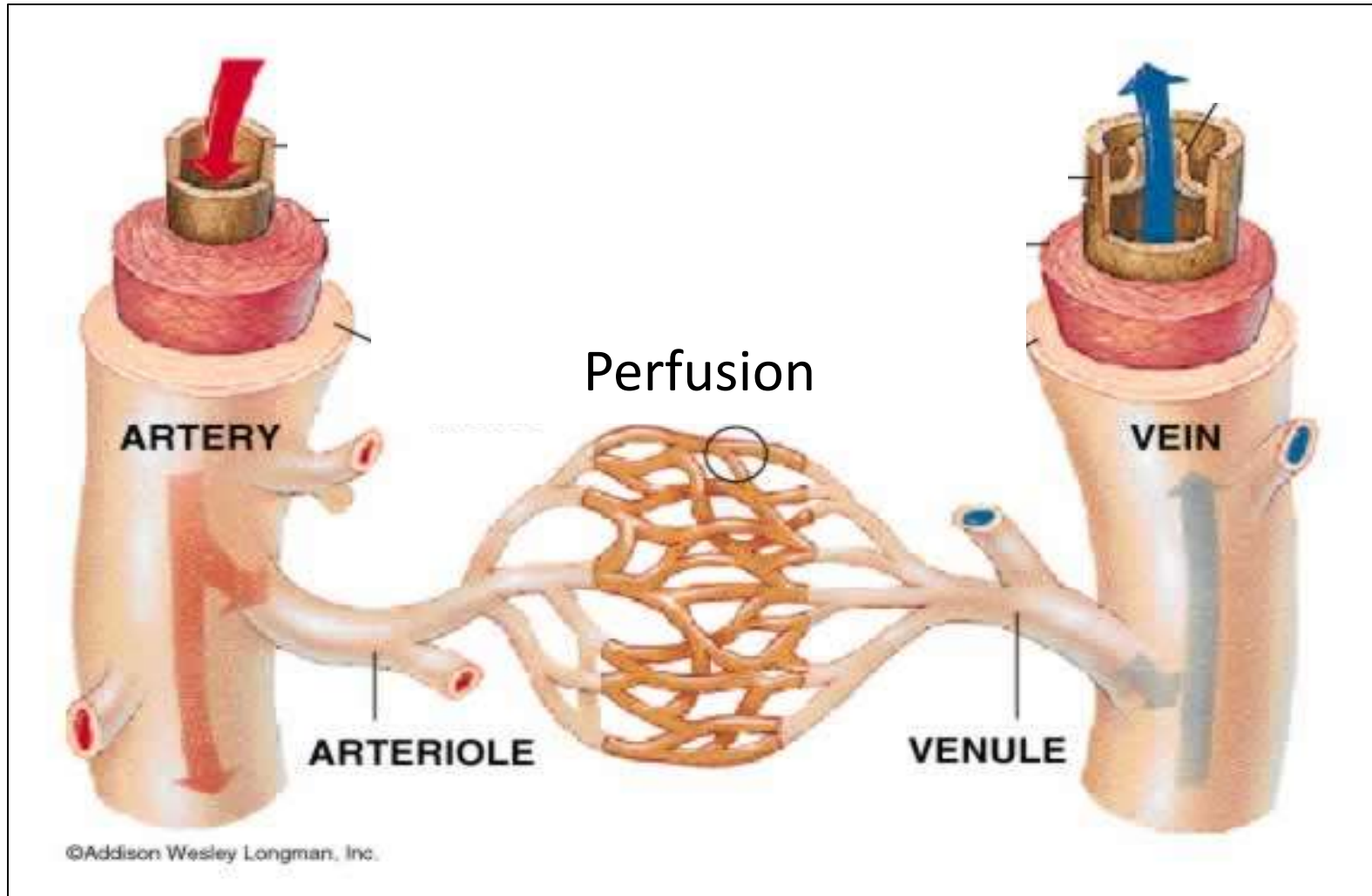


**Figure 1.** Risk factors for definite open-angle glaucoma (OAG; n = 3222). hx = history; PP = perfusion pressure; RR = risk ratio; SBP = systolic blood pressure. \*Based on Cox regression models, adjusting for age, gender, intraocular pressure (IOP), and IOP- and blood pressure-lowering treatment;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

# Methods and Instruments

- Role of Perfusion Pressure ?
  - Role of Venous Pulsation ?
  - Role of IOP and ET-1 on Retinal Venous Pressure ?
  - What is an Ophthalmo-Dynamometer ?
- 



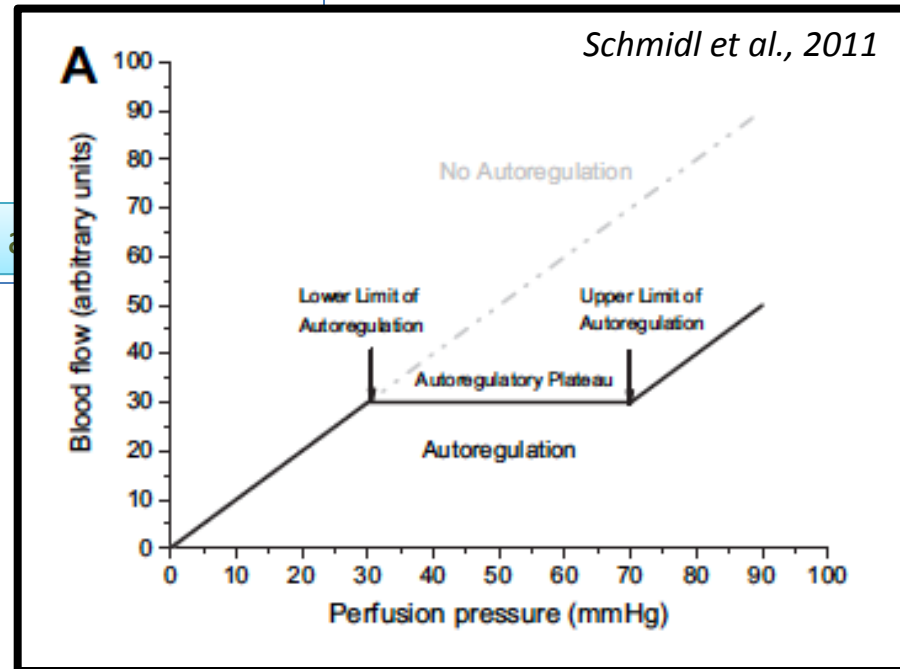


Interconnection between Arteries, Arterioles, Capillaries and Venules  
(Reproduction with Permission of Pearson Education)

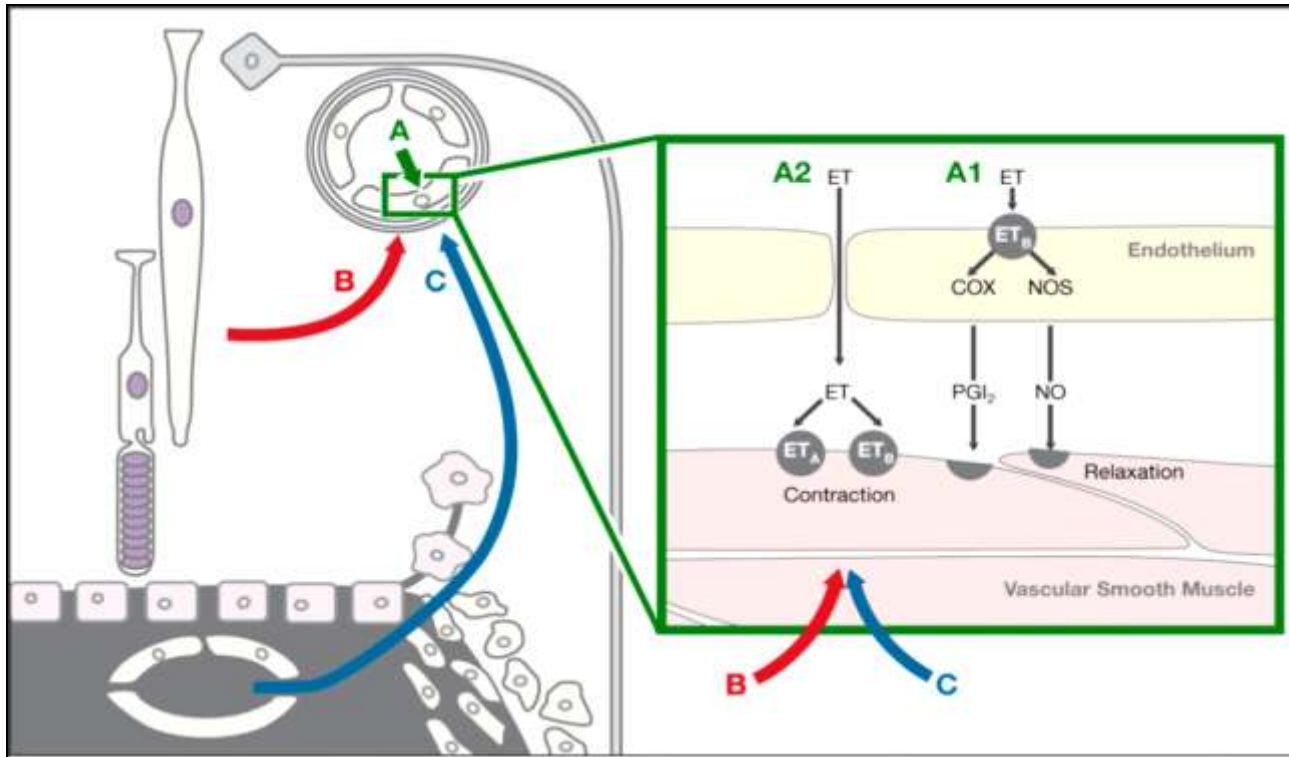
*“Perfusion Pressure is defined as the difference between arterial and venous blood pressure and is the driving force of blood flow.”*

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.

Tissue	Function and characteristics	
Retina	Autoregulation	e.g. Flicker, IOP/ICP, Endothelin-1
Choroidea	No Autoregulation	







B: Hypoxic retina produces ET-1 diffusing to neighboring vessels.

A2: Blood-brain barrier disrupted = ET-1 reaches smooth muscle cells.

C: ET-1 diffuses into the optic nerve head and adjacent retina, leading to vasoconstriction and, thereby, also increases retinal venous pressure.

Flammer, J., et al. (2013). "The primary vascular dysregulation syndrome: implications for eye diseases." *EPMA J* 4(1): 14.

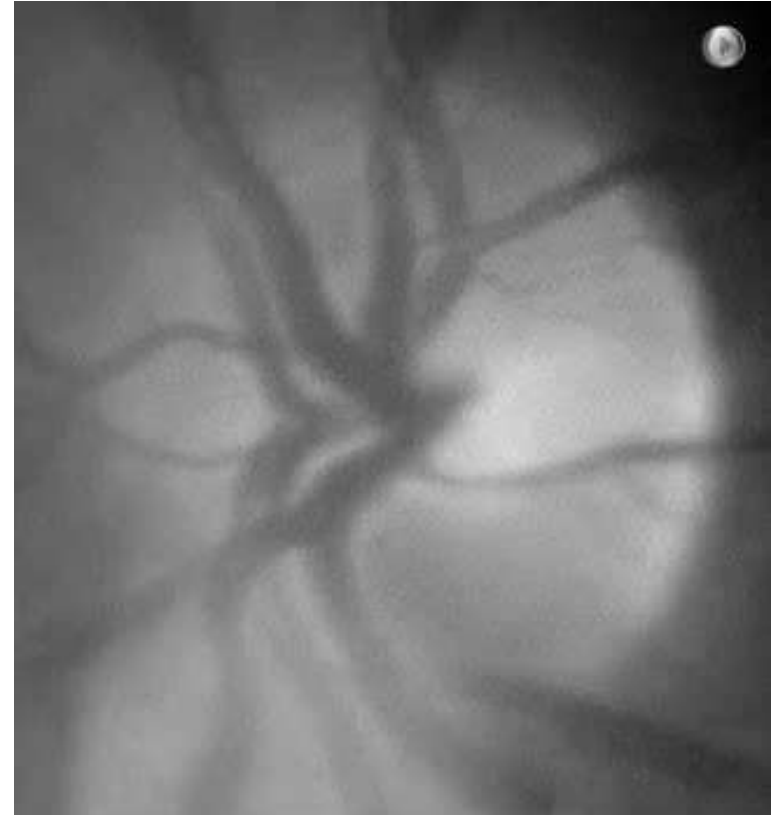
Spontaneous retinal venous pulsation (SVP) occurs at the level of the surrounding IOP.

Prevalence of SVP ? (% of Px)

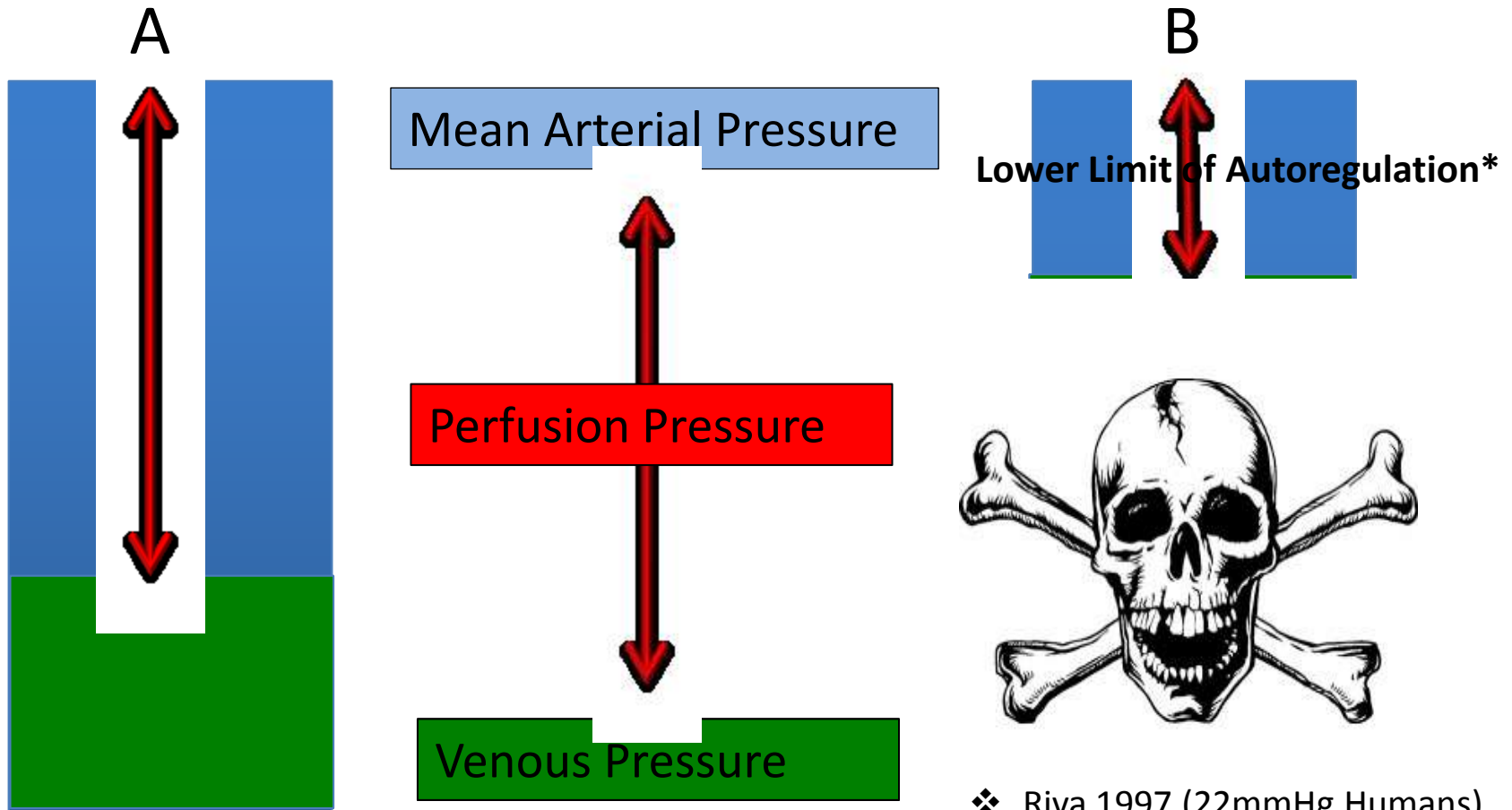
99 %

66 %

33 %



# Relative Contributions of Mean Arterial Pressure and Venous Pressure to Perfusion Pressure



- ❖ Riva 1997 (22mmHg Humans)
- ❖ Riva 1996 (20mmHg Cat's)



*“If we think that perfusion pressure is an important aspect of optic nerve head damage in glaucoma, then we need real measures of ocular and optic nerve head perfusion pressures.”*

Joseph Caprioli, MD

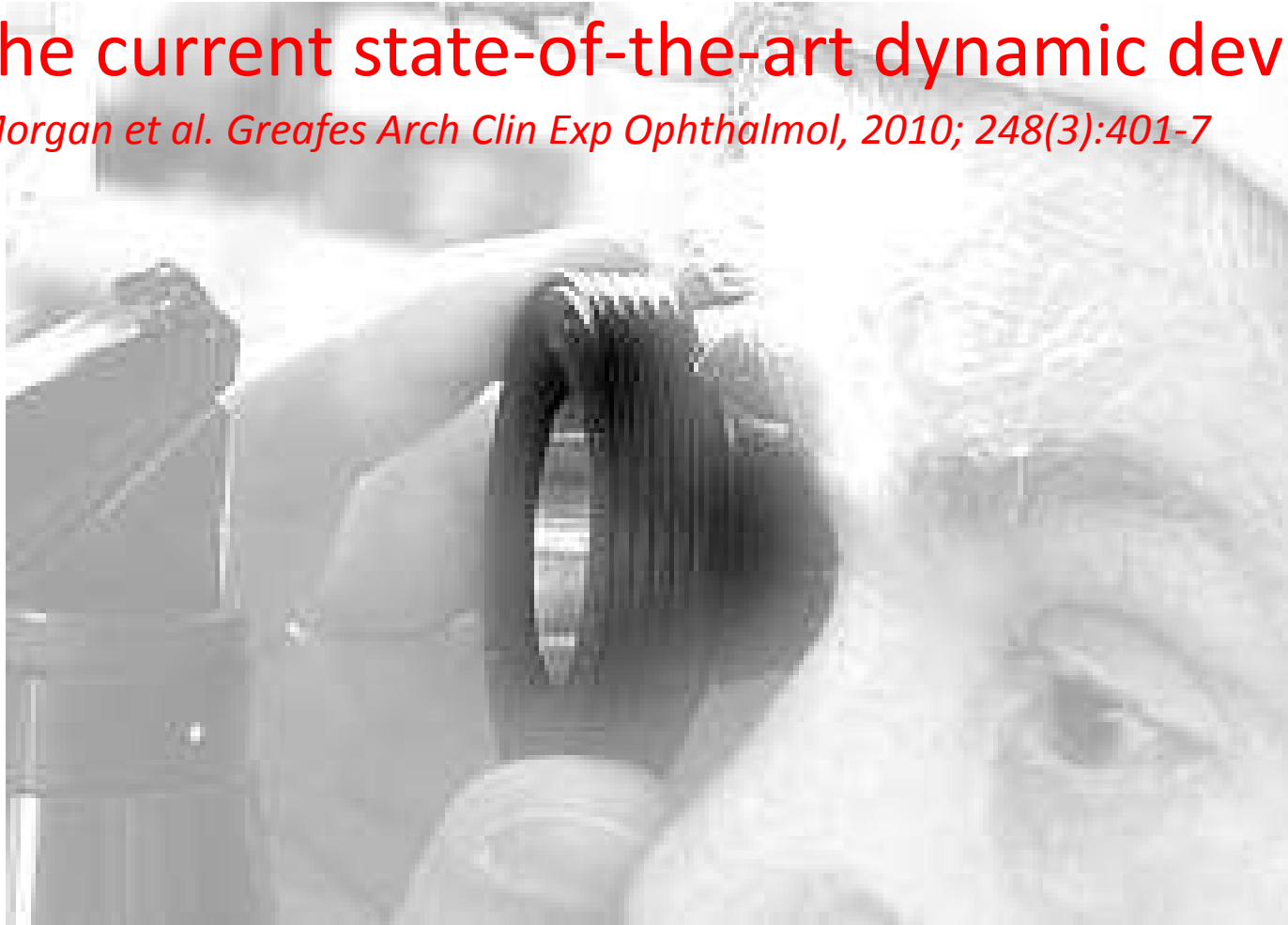
*interviewed by Tony Realin, MD and William Trattler, MD*

*for EyeWorld Online, July 2008*



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

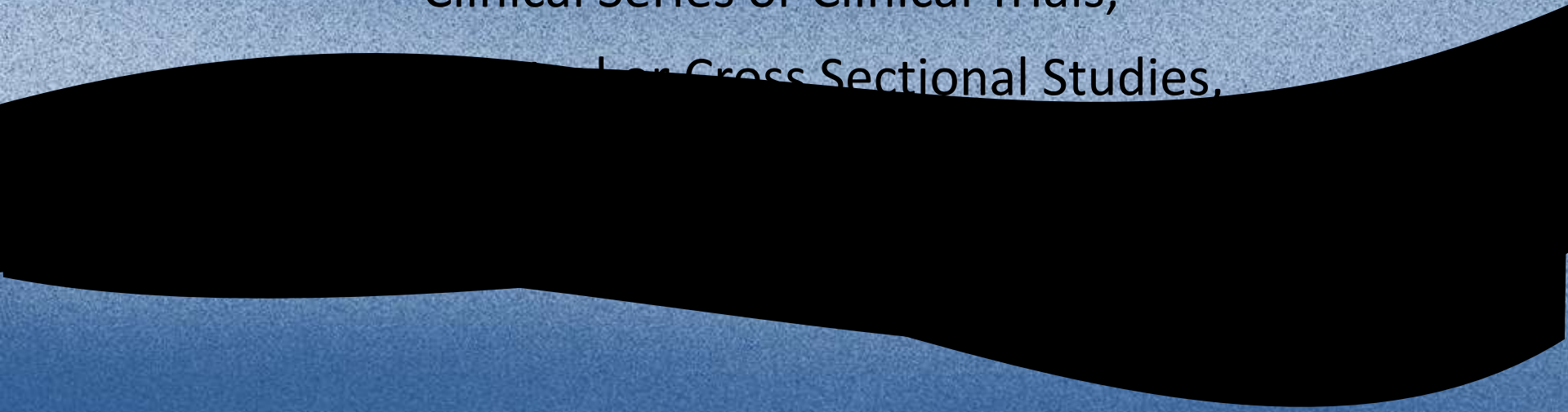
*Morgan et al. Graefes Arch Clin Exp Ophthalmol, 2010; 248(3):401-7*



Ophthalmo-Dynamometry by Dr. Bernhard Loew, Germany

# Hypotheses and Results

Descriptive, Exploratory or Experimental Designs,  
Clinical Series or Clinical Trials,  
and Cross Sectional Studies,





## Aim 2: Retinal Venous Pressure in the non-affected Eye of Patients with Retinal Vein Occlusion

**Goal:** To establish RVP in the affected and the non-affected eye of Px with unilateral retinal vein occlusion compared to healthy controls.

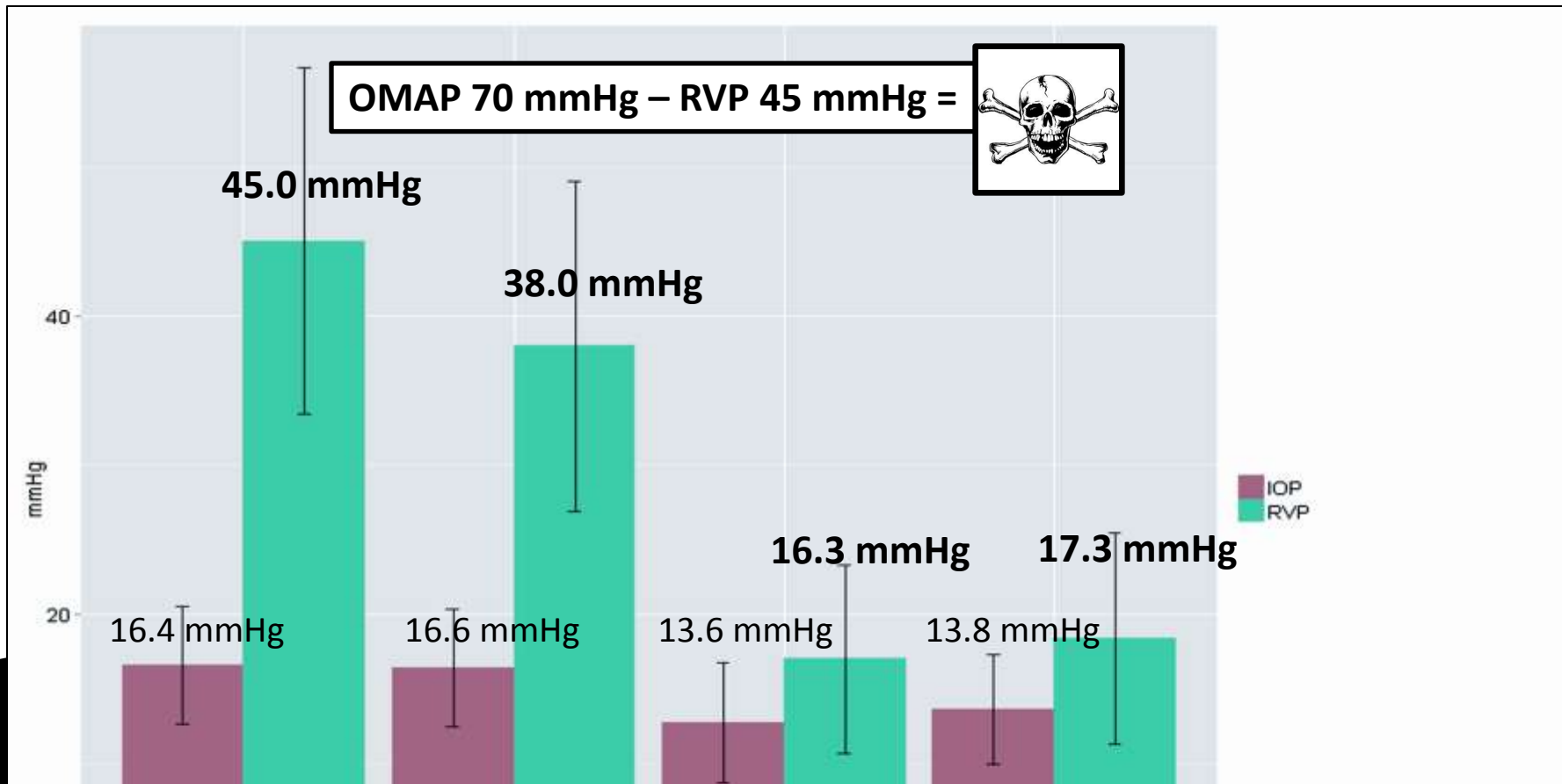
**Method:** Exploratory, case control study

**Statistics:** Descriptive, ANOVA, linear mixed model

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

**Mean age:** 62.8 yo RVO / 61.8 yo controls

## IOP and RVP in Patients and Controls (n = 31/31)



Mean RVP of RVO Px versus healthy controls:

RVO affected eye **+28.2 mmHg** ( $p = >0.001$ )

RVO non-affected eye **+21.2 mmHg** ( $p = >0.001$ )



## Discussion and Conclusion Aim 2

- Retinal venous pressure is significantly increased in the affected AND the non-affected eye of retinal vein occlusion patients compared to healthy controls. Possible Explanations:
- The underlying eye disease affects both eyes but becomes clinically manifest only in the more severe affected eye.

or





# Aim 3: The Effect of Flammer Syndrome on Retinal Venous Pressure in Glaucoma Patients and healthy controls

Goal: To establish RVP in Glaucoma patients and healthy controls with and without 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+ 60.4 yb / 15



# Flammer Syndrome (Konieczka, K. et al. 2014)

- Organs are not well perfused when regulation of blood flow is not adapted to the needs of the tissue.
  - Due to either inappropriate vasoconstriction or insufficient vasodilation. (Konieczka, K. et al. 2014)
  - Primary vascular dysregulation (PVD) by an inborn tendency or secondary due to diseases like multiple sclerosis. (Mozaffarieh, M., 2008)
  - Endothelin-1 blood levels are increased in primary and secondary
- blood flow. (Rachev, M.

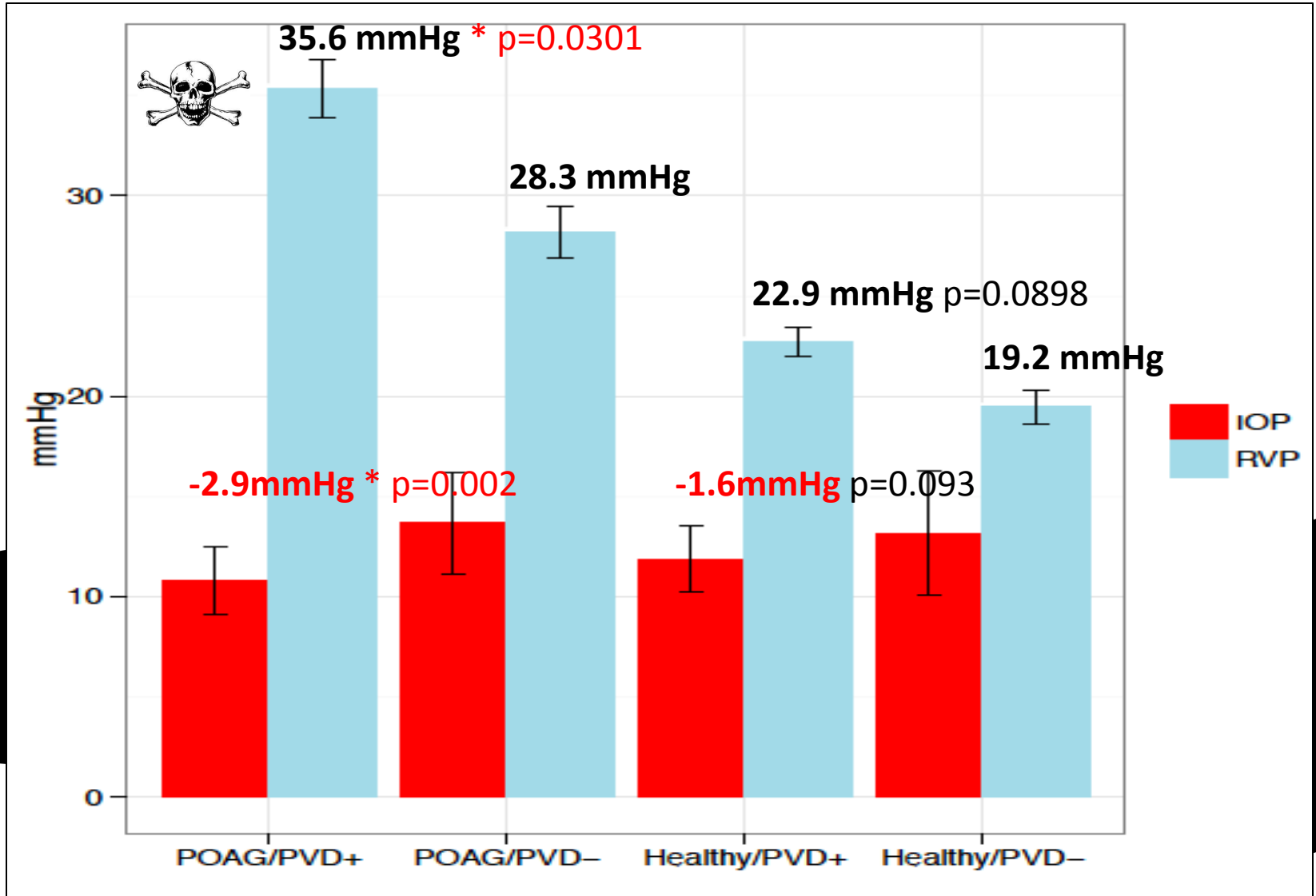
Other typical signs and symptoms:

- Cold feet and hands
- Low blood pressure
- Slim
- Asleep troubles
- Low thirst sensation



By courtesy of Prof. Stodtmeister and Mrs. Kistler.

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





## Discussion and Conclusion Aim 3

- Subjects with Flammer Syndrome (POAG and healthy subjects) had significant higher RVP. ( $p=0.0103$ )
- Subjects with FS had significant lower IOP. ( $p=0.02$ ) Healthy subjects with FS had a tendency to lower IOP.
- Reduced and unstable OPP has been reported to be a risk factor for glaucoma progression. (Pilunat 2014, Choi 2013, Leske 2011, Ramdas 2011, Bonomi 2000)
- Reason for increased RVP: structural changes of the
- Causal relationship of increased RVP and FS needs to be further evaluated.



# Aim 4: Retinal Venous Pressure in Patients with Diabetes

**Goal:** To establish RVP values in diabetic patients with and without diabetic retinopathy compared to healthy controls.

**Method:** Exploratory, cross sectional study

**Statistics:** Descriptive, ANOVA, linear mixed model

**Population:** 20 non-DR, 27 DR and 127 healthy subjects

University Hospital Basel

**Gender:** non-DR 30.0% w / 70.0% m

DR 29.6% w / 70.4% m

Age matched

Controls 64.6 yo

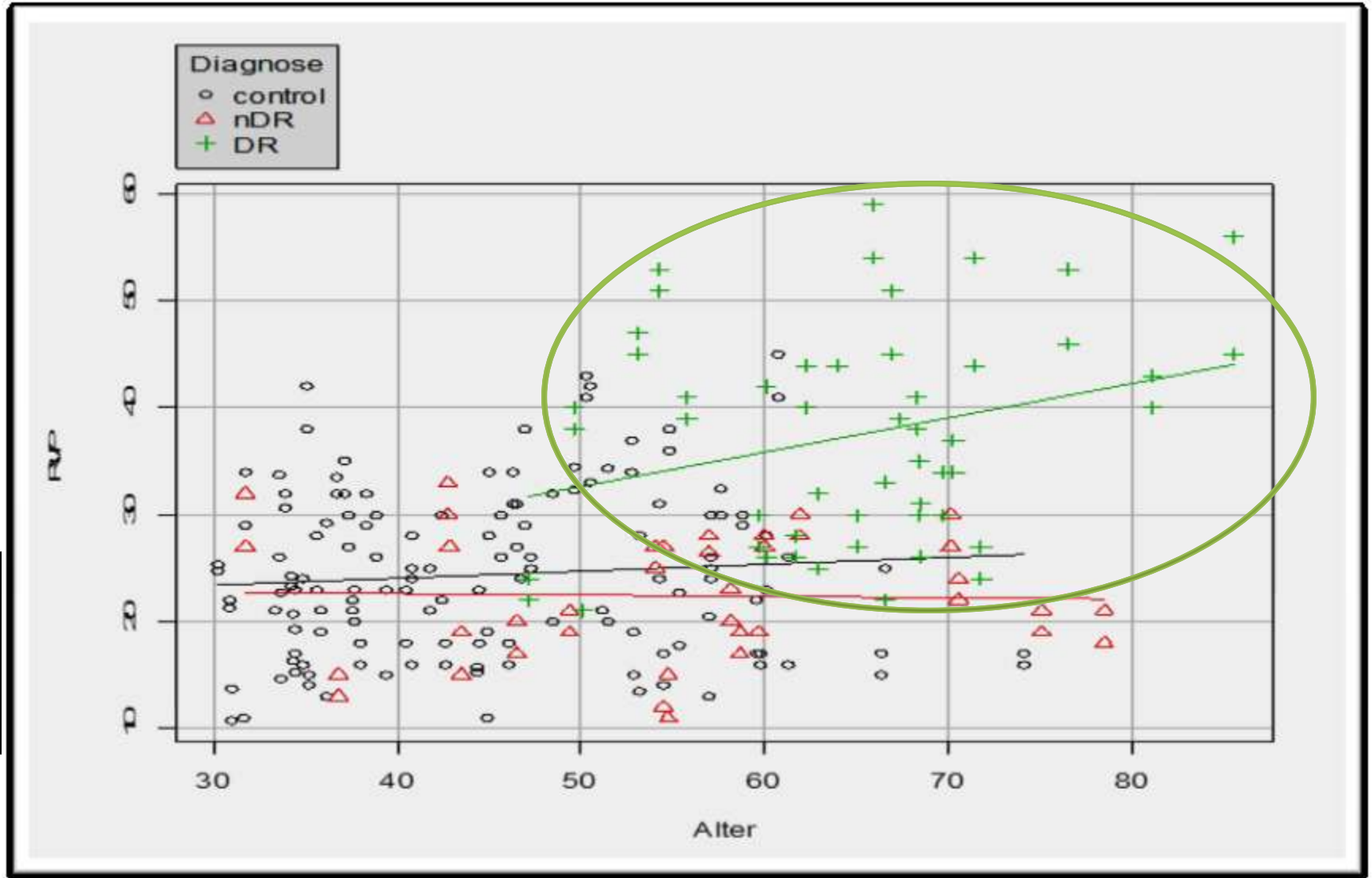
## Descriptive statistics RVP and Diabetes

	control n=127	nonDR n=20	DR n=27	p overall
Age				
IOP				
RVP				
Gender				
- female				
- male				
Eyes				<0.001
with SVP	43 (16.9%)	9 (22.5%)	0 (0%)	
Non-SVP	211 (83.1%)	31 (77.5%)	54 (100%)	

## Descriptive Statistics of AGE-matched Data


	<b>control</b> n=14	<b>nonDR</b> n=20	<b>DR</b> n=14	<b>p overall</b>
Age	58.5 (7.28)	55.3 (12.3)	58.6 (7.02)	0.55
IOP	14.9 (3.18)	15.3 (3.27)	15.9 (2.27)	0.319
RVP	25.2 (9.11)	22.5 (5.78)	33.8 (9.81)	0.0076

RVP versus Age for each study group (all subjects)





## Discussion and Conclusion Aim 4

- None of the DR patients showed SRVP.
  - RVP in DR is significantly higher than in non-DR ( $p=0.004$ ) and in healthy controls ( $p=0.040$ ).
  - Reason for increased RVP: structural changes of the ONH and/or local dysregulation of retinal veins due to increased ET-1 ?
  - Causal relationship of increased RVP and ET-1 in DR needs to be further evaluated.
- 




# Overall Summary, Discussion and Conclusion




# Disputing Monks, Sera Monastery / Tibet 2013





1. Retinal venous pressure (RVP) is an essential factor in the establishment of effective retinal perfusion pressure.
  2. RVP can be established precise, reproducible, quick and cost-effective by Ophthalmo-Dynamometry.
  3. RVP is increased in ocular diseases such as glaucoma, diabetic retinopathy and retinal vein occlusion.
  4. RVP is increased in subjects with Flammer-Syndrome.
- 



5. Ocular perfusion pressure (OPP) of subjects with FS is lower than in subjects without FS.
  6. The physiological reaction to RVP in environmental hypoxia takes longer than 2 hours.
  7. Constant environmental hypoxia increases RVP and lowers OPP despite mean arterial pressure increase.
  8. Tx: Lifestyle, Nutrition and Drug treatment ->
- 

www.flammer-syndrome.ch

HOME EN DE

## Flammer Syndrome

DEFINITION

TERMINOLOGY

SYMPTOMS

ASSOCIATED 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 little research has been conducted on treatment, we can still assist these patients based on the information available. The treatment is based on three pillars: (a) lifestyle management, (b) nutrition, and (c) drug therapy.

**Lifestyle management**  
Most subjects with Flammer syndrome know what triggers their vasoconstriction. We can recommend ways to avoid those. These can be: avoid stress, avoid excessive alcohol consumption and regular but not excessive physical activity. Relaxation techniques like yoga and Tai Chi can help to relax. Exercise should be avoided in the evening to avoid excessive nocturnal blood pressure dips. Omega-3 fatty acids, as contained in fish, 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 (I) 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 500mg / Tag**

Drug Treatment: Low-dose Calcium channel-Blocker (e.g. Nifedipin) and Magnesium are recommended for clinical use to lower retinal venous pressure.

- ❖ Cybulska-Heinrich et al., Value of non-IOP lowering therapy for glaucoma. *Klin Monbl Augenheilk* 2013; 230(2); 114-19
- ❖ Mozaffarieh, M., The Effect of Nifedipine on Retinal Venous Pressure of Glaucoma Patients with Flammer-Syndrome: *Graefe's Archiv* 2015: in press

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

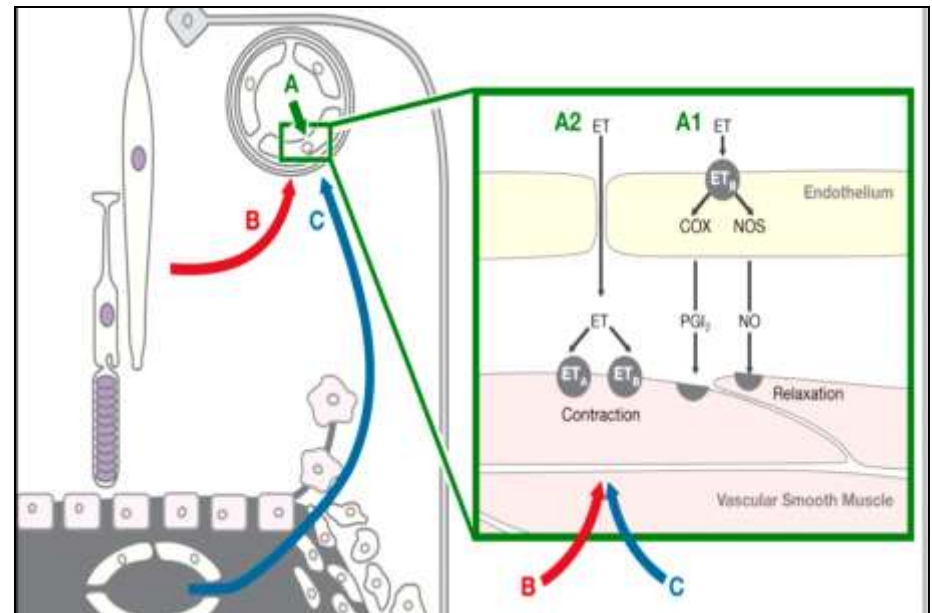
(1) Cellini, M. et al. 2012; Kaiser, H. et al. 1995

(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






What do diabetic and glaucoma patients have in common with (dead) mountaineers on high mountains?



Answer: The possibility of becoming blind (or even die) due to hypoxia

# Take-Home !

- Retinal venous and ocular perfusion pressure are evident.
  - If no spontaneous retinal venous pulsation is noticeable,  
RVP is higher than intraocular pressure and has to be  
established to complete the clinical picture.
  - Hypoxia does have an influence on RVP.
  - Start to look for retinal venous pulsation and pressure !
- 

# Ophthalm-Dynamometer : IMEDOS GmbH, Jena, Germany



The Pioneer of Retinal Vessel Analysis

[Company](#)

[Products](#)

[Experts](#)

[Presse](#)

[Service](#)

[Events](#)

[Fundus Imaging](#)

[Static Vessel Analysis](#)

[Dynamic Vessel Analysis](#)

[Network Solutions](#)

[Animal Experimentation  
Systems](#)

[Ophthalmodynamometry](#)

## Ophthalmodynamometry

### Contact Lens Dynamometer (after Loew)

The contact lens dynamometer (after Loew) can be used among others for the measurement of retinal venous pressure.

In the past it was produced and sold by the company Meditron GmbH. As of June 2014 the production and distribution was taken over by Imedos Systems UG.

Information about the product can be found [on the website of Meditron](#).



Deutsch  | English 

**SEARCH**

[GO](#)

**CONTACT**

IMEDOS Systems UG  
(haftungsbeschränkt)  
Am Nasstal 4  
D-07751 Jena  
GERMANY

phone: +49-3641-63960  
fax: +49-3641-639612

[info\(at\)imedos.de](mailto:info(at)imedos.de)

[Contactpage »](#)



## Mentors:

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

## SALUS GPBI / USA

- Dr. William Monaco
- Asami Kojima
- Teachers and consultants
- Leaders and staff at SALUS

## University Hospital Basel / Switzerland

- Ethic Committee Basel (EKBB)
- University Eyeclinic Basel and staff



- Examiners
- My family !
- Eyeness AG and staff