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

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Declaration

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 !!

Goals:
- Reproducible
- Observer controlled
- Easy to use
- Observation & documentation
- System Tonometric
- Portable
- Multi use

Abbreviations:
- ODF: ocular fundus
- VPD: primary venous pressure
- VEGF: vascular endothelial growth factor
- VSMC: vascular smooth muscle cells
- ORA: ocular response analyzer

Risks for RVO:
- Mechanical injury
- Thrombosis
- Hypoxia

Central vein pressure:
- Glaucoma
- Increased IOP
- Decreased systemic blood pressure
- Venous resistance
- Reflux microvascular resistance

Mechanisms:
- Increased venous pressure
- Venous hypertension
- Hypoxia of retinal tissue
Introduction
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

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.”

Epidemiological and Clinical Evidence
## Global Epidemiological Evidence

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients</th>
<th>Prevalence</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glaucoma</td>
<td>64.3 mio</td>
<td>3.54% (40-80yo)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>387.0 mio</td>
<td>8.30% (all ages)</td>
<td></td>
</tr>
<tr>
<td>Vein Occlusion</td>
<td>16.4 mio</td>
<td>0.52% (20yo+)</td>
<td></td>
</tr>
<tr>
<td>High Altitude Sickness</td>
<td>n.A.</td>
<td>42% (3000m/9’842ft)</td>
<td>1.5% - 38% !</td>
</tr>
</tbody>
</table>

### References:


Eberhard Jurgalsky for 8000ers.com, 2008
Altered Retinal Venous Pressure is published for:

- **Glaucoma**  

- **Vein occlusion**  
  *(Mozzafarie et al. 2014, Yasuda 2010, Jonas 2007)*

- **Flammer Syndrome**  
  *(Mozzafarie et al. 2014)*

- **Diabetes**  
  *(Cybulksa 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, Suh-Yuh Wu, MA, Anselm Hennis, FRCP(UK), PhD, Robert Honkaniemi, MD, Barbara Nemesure, PhD, 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)
Role of Perfusion Pressure

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

### Retinal versus choroidal blood flow

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Function and characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retina</td>
<td>Autoregulation e.g. Flicker, IOP/ICP, Endothelin-1</td>
</tr>
<tr>
<td>Choroidea</td>
<td>No Autoregulation</td>
</tr>
</tbody>
</table>

Schmidl et al., 2011
Influence of ET-1 on Vasoconstriction

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.

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

- **Mean Arterial Pressure**
- **Perfusion Pressure**
- **Venous Pressure**

**A**

**B**

- **Lower Limit of Autoregulation**
  - 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, ... "


Ophthalmo-Dynamometry by Dr. Bernhard Loew, Germany
Hypotheses and Results

Descriptive, Exploratory or Experimental Designs,
Clinical Series or Clinical Trials,
Case Control or 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 / 62.6 yo controls
Results Aim 2
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.
  - RVP is increased due to systemic factors such as increased ET-1.
  - Further studies are needed to clarify this.
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 yo / FS- 56.6 yo
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 vascular dysregulation reducing blood flow. (Pache, M. et al., 2003)
- Combination of PVD and a cluster of vascular and non-vascular signs and symptoms are called “Flammer Syndrome.”
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. Kristie
Results Aim 3

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>IOP</th>
<th>RVP</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>POAG/PVD+</td>
<td>35.6 mmHg</td>
<td>28.3 mmHg</td>
<td>0.0301</td>
</tr>
<tr>
<td>POAG/PVD-</td>
<td>22.9 mmHg</td>
<td>19.2 mmHg</td>
<td>0.0898</td>
</tr>
<tr>
<td>Healthy/PVD+</td>
<td>-2.9 mmHg</td>
<td>-1.6 mmHg</td>
<td>0.002</td>
</tr>
<tr>
<td>Healthy/PVD-</td>
<td>-1.6 mmHg</td>
<td>-1.6 mmHg</td>
<td>0.093</td>
</tr>
</tbody>
</table>
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 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.
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
### Results Aim 4

#### Descriptive statistics RVP and Diabetes

<table>
<thead>
<tr>
<th></th>
<th>control</th>
<th>nonDR</th>
<th>DR</th>
<th>p overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=127</td>
<td>n=20</td>
<td>n=27</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IOP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyes</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>with SVP</td>
<td>43 (16.9%)</td>
<td>9 (22.5%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Non-SVP</td>
<td>211 (83.1%)</td>
<td>31 (77.5%)</td>
<td>54 (100%)</td>
<td></td>
</tr>
</tbody>
</table>
## Results Aim 4

### Descriptive Statistics of AGE-matched Data

<table>
<thead>
<tr>
<th></th>
<th>control</th>
<th>nonDR</th>
<th>DR</th>
<th>p overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>14</td>
<td>20</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>58.5 (7.28)</td>
<td>55.3 (12.3)</td>
<td>58.6 (7.02)</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>IOP</strong></td>
<td>14.9 (3.18)</td>
<td>15.3 (3.27)</td>
<td>15.9 (2.27)</td>
<td>0.319</td>
</tr>
<tr>
<td><strong>RVP</strong></td>
<td>25.2 (9.11)</td>
<td>22.5 (5.78)</td>
<td>33.8 (9.81)</td>
<td>0.0076</td>
</tr>
</tbody>
</table>
Results Aim 4

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
Summary and Discussion

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.
Summary and Discussion

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

- Cybulksa-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
Discussion: Evidence of 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.

(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!
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.
Acknowledgments

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- Eyeness AG and staff