Constantly regulated hemodynamics assuming delivery of O2 and metabolic substrates, as well as intact blood-retinal barriers are necessary requirements for the maintenance of retinal structure and function.

The neuronal cells maintain energy state through the formation of ATP, produced by means of two fundamental metabolic pathways, glycolysis and oxidative phosphorylation.

These energy generating reactions, consuming O2 and metabolic substrates, are essential for neuronal function (Na+/ K+, Glutamate).

1. Retinal circulation
- Derives from the central retinal artery
- Is an end-arterial system without anastomose
- Capillaries form an inter-connecting two layer pattern
- 3rd layer of radial peri-papillary capillaries

Techniques for measuring the retinal blood flow
- Quantitative determinations of BF in animals.
  - Radioactively labeled microspheres.
  - Radioactive krypton desaturation.
  - Hydrogen clearance.
  - Laser speckle phenomenon.
  - Targeted dye delivery.
  - Leukocyte dynamics by fluography.
  - Invasive laser Doppler flowmetry.
Techniques for measuring the retinal blood flow

Non-invasive techniques used in clinical research

Bidirectional laser Doppler velocimetry (BLDV)

\[
V_{\text{mean}} = \frac{V_{\text{max}}}{2} \]

BLDV is based on the Doppler effect.

Measurements of the diameter (D) of retinal vessels:
- Fundus photographs
- Retinal Vessel Analyzer (RVA)
- Continuous recording of D changes (dynamic measurements)

Retinal circulation
- Low level of flow (4% of total ocular BF)
  - In primates: 25–50 ml/min/100g tissue
  - Human total retinal BF: 40.8–52.9 µl/min
- High O₂ extraction (40%)

Choroidal circulation
- 85% of total ocular blood flow
- Low O₂ extraction (3-4%)
- 60% of O₂ and 75% of glucose of retinal needs

2. Regulation of the retinal blood flow

Autoregulation:
- "the ability of a tissue to adapt blood flow to metabolic needs"
- Achieved by the modifications of the resistant vessels tone
  i.e. arterioles, capillaries

\[
F = \Delta P_{\text{pm}} \times \pi \frac{D^4}{8nL} \]

F is correlated to the vessels diameter

Determinants of retinal vessels Diameter

Systemic determinants
- Innervation
- Blood gases i.e. PaO₂, PaCO₂
- Circulating molecules

Local determinants
- Substances affecting the tone of smooth muscle cells and pericytes released by
  - the vascular endothelium
  - Neuro-glial activity
Mechanisms of the retinal BF regulation

Metabolic mechanism

- Neuro-glial signalling: nNOS/lactate/PGs
- Retinal Relaxing Factor (ET receptors?)

Myogenic mechanism

Endothelial cells
- Relaxation: NO/PGI2/ETB1
- Contraction: ET1 (ETA/ETB2)/TXH2

3. Autoregulation of the retinal blood flow

Blood flow constant during variations of PPm

PPm: MOAP - IOP

Autoregulation to a MABP up to 41%

Blood flow response to visual stimulation

Flicker-induced change of diameter of retinal vessel, measured by RVA.

Blood flow response to Blood gases

Hyperoxia

- Hyperoxia on the D of retinal arteries in the four quadrants of the fundus
- 60% decrease of the RBF

The retinal hemodynamic alterations affect:

- the delivery of the retinal O2 and metabolic substrates,
- the integrity of the blood-retinal barriers,
- Ischemia, tissue hypoxia and intracellular edema
- Blood flow dysregulation leads to BRB barriers breakdown and extra-cellular edema
Hypertensive retinopathy
Narrowed retinal arterioles are associated with long term risk of HTA. Structural alterations of the microvasculature/impaired regulation may be linked to the development of hypertension. Wong T Y et al., Br J Ophthalmol 2007
Endothelial function of the retinal vasculature is impaired in early essential hypertension. Can be improved by AT1-receptor blocker Delles C, et al., Stroke 2004

Diabetic retinopathy
Altered myogenic and hyperoxic response of retinal arterioles Blum M et al., Ophthalmologe 2003 and 2006
Decreased retinal BF occurs in PDR and RVO Grunwald et al. 1993, Avilla et al., 1998
Retinal BF decrease and dysregulation
Arteriolar sclerosis
Rheologic factors
Thrombosis
Hemodynamic

Increased circulating ET-1 levels in patients with RVO may be a marker of the occlusive event

ET-1 plasma levels
Normals 7.90 ± 1.6 pg/ml; p < 0.05
HTA 8.50 ± 2.9 pg/ml; p <0.05
RVO 14.22 ± 4.6 pg/ml
RVO isch. 16.97 ± 3.5 pg/ml; p < 0.01

Exp. Microangiopathy
Decrease in arteriolar diameter
1 hour 22.8 ± 3.8%
2 hours 25.4 ± 3.4%
leading to tissue hypoxia

RVO: Circulation Modifications
Decreased arteriolar flow
NO decrease
Myogenic vasoconstriction / ET

A significant increase in retinal arteriolar diameter was demonstrated after juxta-arteriolar BD-123 microinjection in healthy and in acute BVO-minipig retinas.
The results suggest a role for endothelin-1 in maintaining retinal basal arteriolar tone.
Retinal vein occlusions: The potential impact of a dysregulation of the retinal veins.


Atherosclerosis and vascular dysregulation: Due to alterations to the arterial wall and its adventitia, Endothelin-1 is overexpressed in endothelial cells and by cells of the surroundings of the atherosclerotic arteries. As consequence, the vein constricts and in extreme situations a RVO results.

Vaso-permeability factors and macular edema: tissue hypoxia and VEGF

Macular edema: Inciting molecules
- Prostaglandins
  - PGE1
  - PGE2
  - PGF2α
- Leukotrienes
  - LTb4
  - LTC4
  - LTD4
- Nitric oxide
- Cytokines
  - IL-1β
  - TNF-α
  - IL-6
  - IGF-1
  - SDF-1
  - ICAM-1
- Inhibition of VEGF signaling causes loss of endothelial fenestrations and regression of tumor vessels.

VEGF expression and BRB changes

Increased in BRVO
Correlated to macular edema

Hypoxia and VEGF induce permeability through rearrangement of endothelial junctional proteins.

Diabetic retinopathy

The structural alterations of the retinal vessels in diabetes are attributed to:
- vascular endothelium injuries
- dysfunction of flow and/or the flow regulation

Inhibition of VEGF signaling causes loss of endothelial fenestrations and regression of tumor vessels.

Noma et al., Am J Ophthalmol 2005


Inai T. et al., American Journal of Pathology 2004

VEGF expression and BRB changes

Retinal arteriolar dys-regulation  →  Vasodilatation

- **Poiseuille Law**
  - capillaries and veinules
  - intra-luminal pressure increase

- **Sterling Law**
  - Capillaries and venular dilatation, increase of vessels length and tortuosity

- **Laplace Law**
  - Increase of exudation and reduction of re-absorption

**Diabetic retinopathy**
Abnormal regulation of the RBF

**Vasoconstriction of retinal arterioles with oxygen breathing in DR**
Blum M et al., Ophthalmologe 2003
· 100:306–309

**Group I**
-6.2% (±4.0)

**Group II**
-6.1% (±2.8)

**Group III**
6.6% (±4.1)

**Group IV**
+2.5% (±4.7)

**Group I:** no DR / **Group III:** moderate/severe NPDR + laser
**Group II:** mild/moderate DR, **Group IV:** PDR with laser tr.

**The myogenic response of retinal arterioles in diabetic retinopathy**
Blum M et al., Ophthalmologe 2006
· 103:209–213

**PDR: recovery of flow regulation**
PRP and arteriolar vasoconstriction

**Oxygen and recovery of flow regulation**
PRP and blood flow regulation

Decrease of the retinal blood flow under hyperoxia
Normals 60%
Riva et al., 1983
PDR 20% +/- 15%
Grunwald 1986
PDR + laser 45% +/- 12%
Grunwald 1986

Recovery of blood flow regulation following PRP

**Conclusions**

The vascular tone of the resistant vessels (arterioles, capillaries) in the retina is modulated by the interaction of multiple mechanisms affecting the arteriolar smooth muscle and the vascular pericytes.

The retinal blood flow is autoregulated by the interaction of myogenic and metabolic mechanisms through the release of vasoactive substances by the retinal tissue surrounding the arteriolar wall and/or the vascular endothelium.

**Conclusions**

The interaction of metabolic pathways is implicated in the control of the vasomotion and autoregulation in the inner retina in order to maintain constant the retinal blood flow.

Impairment of structure and function of the retinal neuronal tissue and endothelium leads to the retinal blood abnormal regulation observed during the evolution of ischemic microangiopathies.