

REPERFUSIONSSCHADEN

Theorie und klinische Praxis

H. Rabl

Abtlg. für Chirurgie Leoben

Reperfusion - Syndrom

Le Cormier 1954

K^+ ↑

Exitus letalis

Reperfusionsschaden

Reperusionsparadox

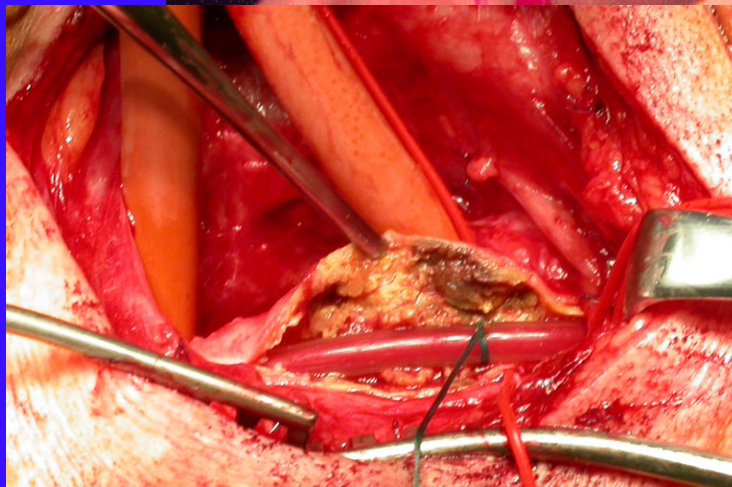
Zu beobachtende Pathologie (funktionell,
ultrastrukturell, klinisch) nach
wiederhergestellter Durchblutung eines zuvor
minderversorgten Organs, von Organsystemen
od. eines Organismus

Reperfusionsschaden

- Transplantationsmedizin
- Kardiologie (Behandlung des Myocardinfarkt)
- Neurologie (Behandlung des Schlaganfalls)
- Gefäßchirurgie (Revaskularisationsoperationen)
- Traumatologie (Schockbehandlung, WB von Unterkühlten)
- Viszeralchirurgie (Leber, Darmoperationen)
- Nephrologie

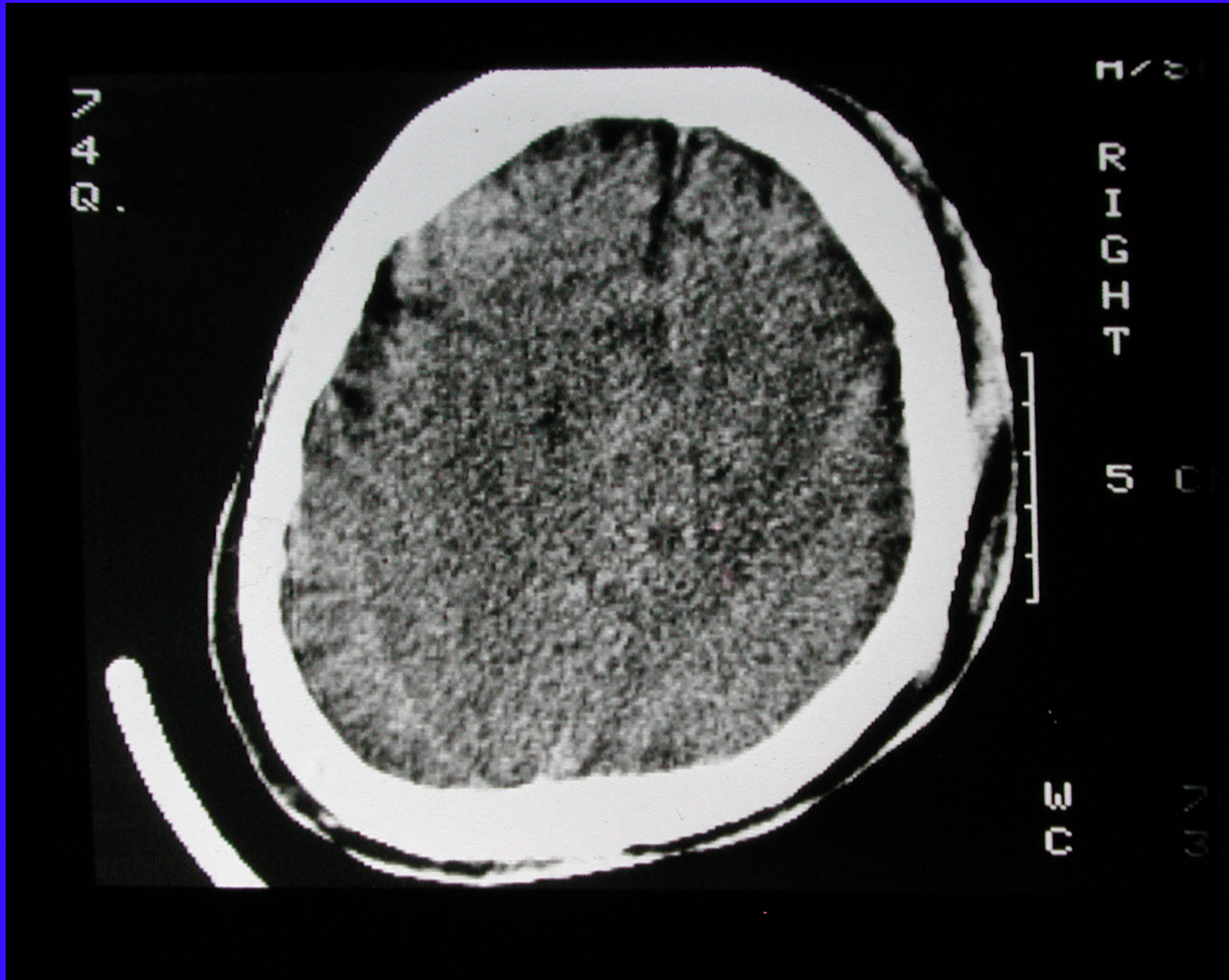


Hypertonus
Cephalea

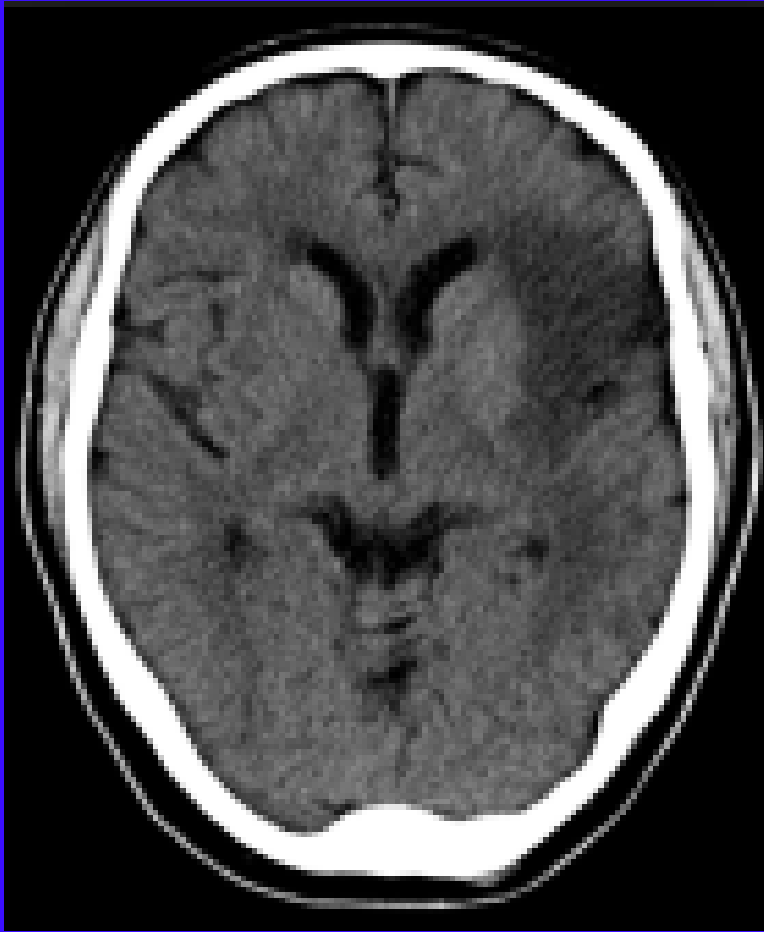


Rabl H. et al. Diminished production of malondialdehyde after carotid artery surgery as a result of vitamin administration. Med. Sci. Res. 1996; 24: 777- 80

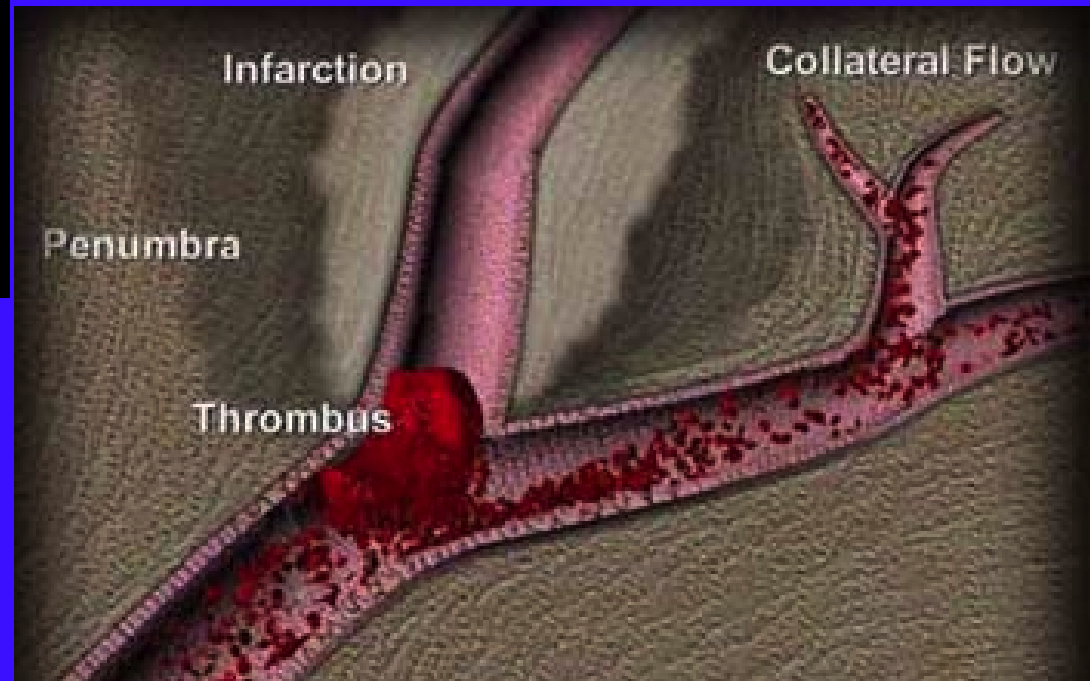
Hirnödem



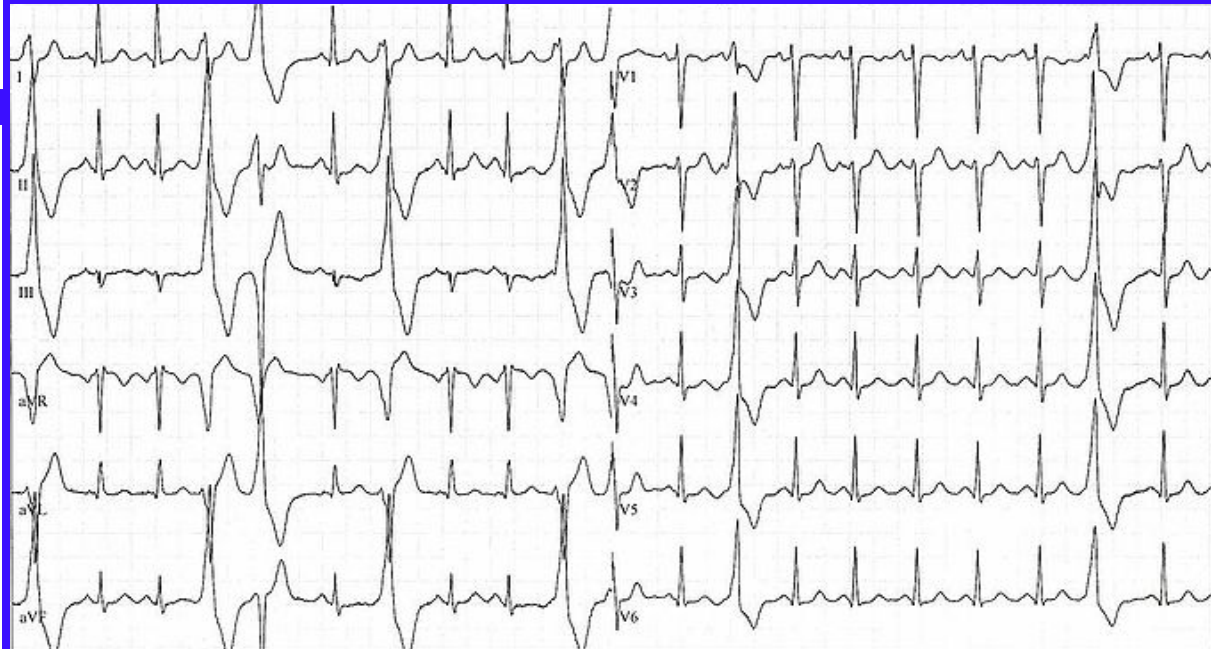
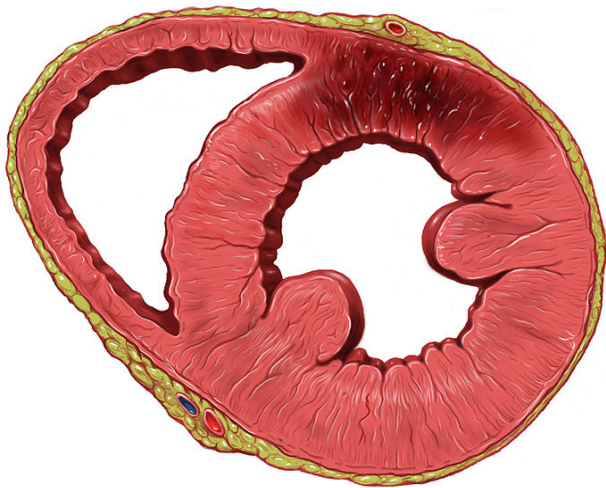
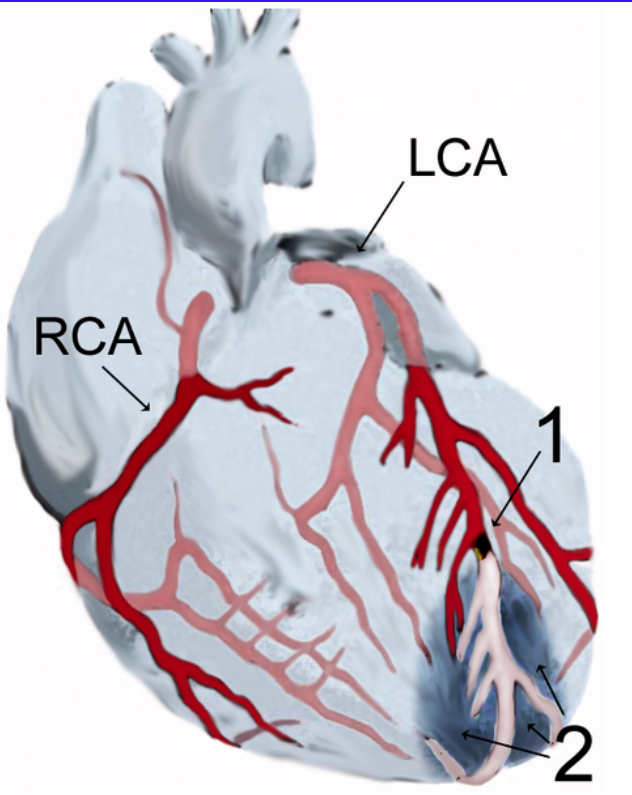
Europaweit 350.000 CPR / a
2 – 10% ohne neurolog. Komplikationen



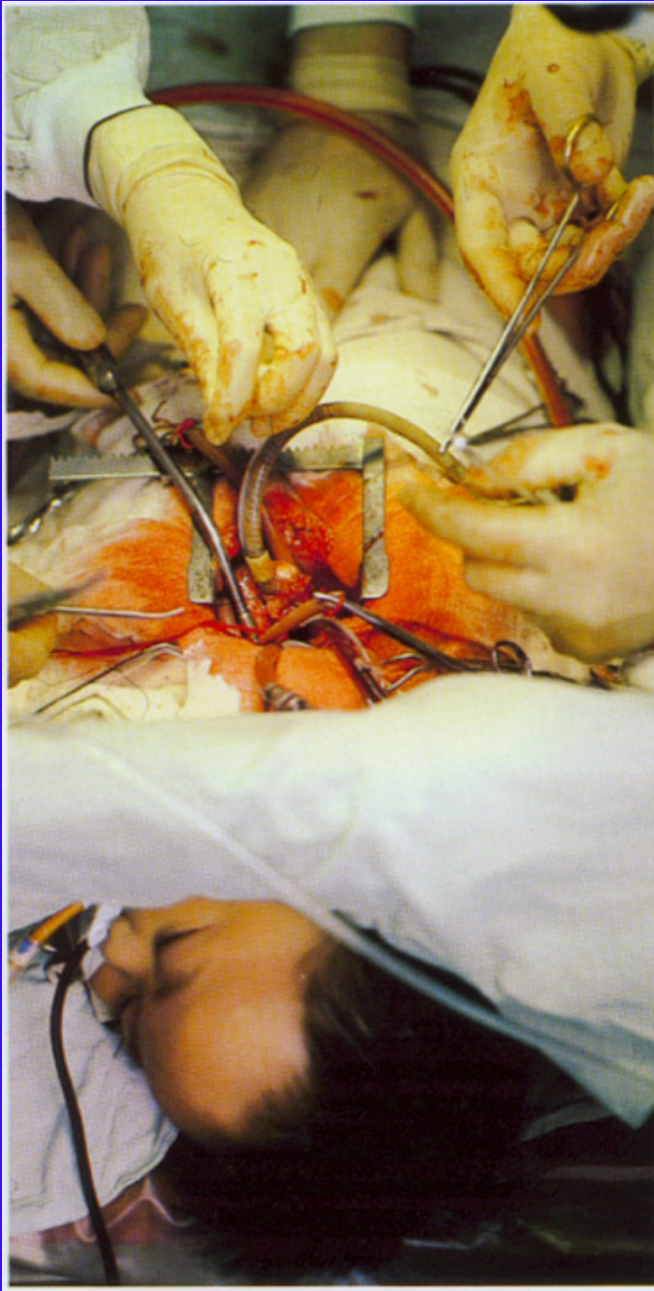
Zunahme sensomotorischer und kognitiver Funktionsstörungen nach erfolgreicher Thrombolyse



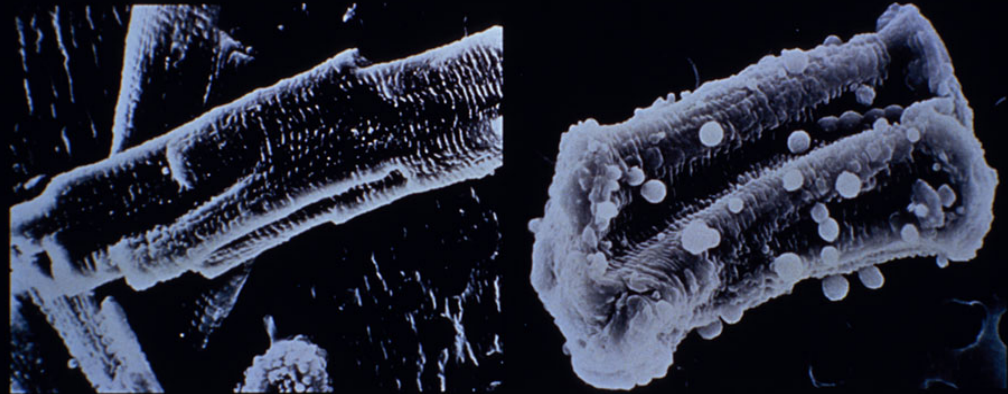
Reperfusion – Arrhythmien nach Thrombolyse / PTCA



Stunned myocardium syst. Kontraktionsstörung



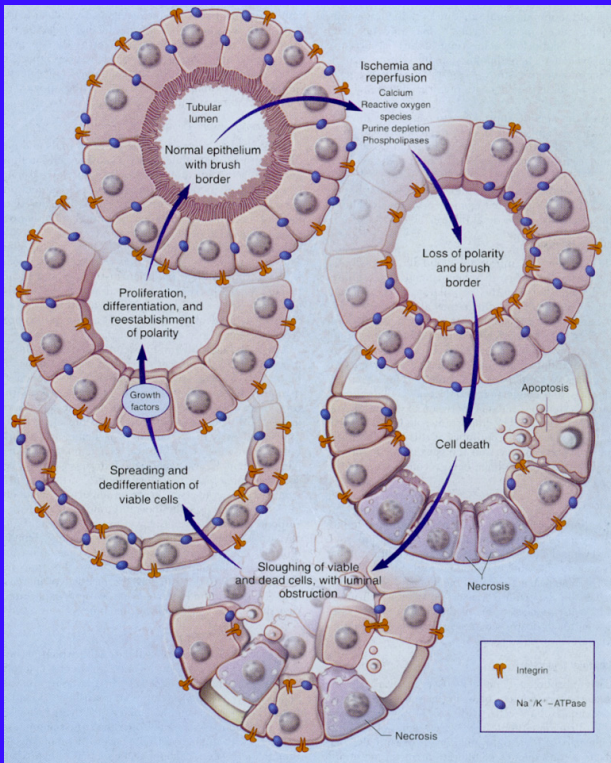
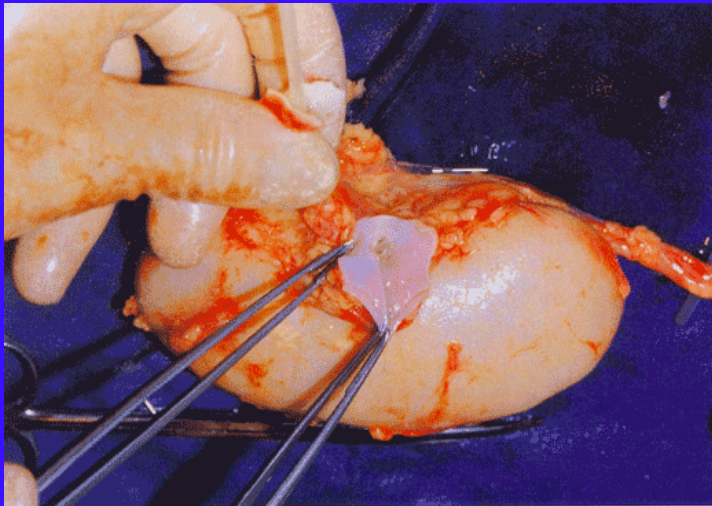
Lipid peroxidation as a mechanism of injury to heart cells



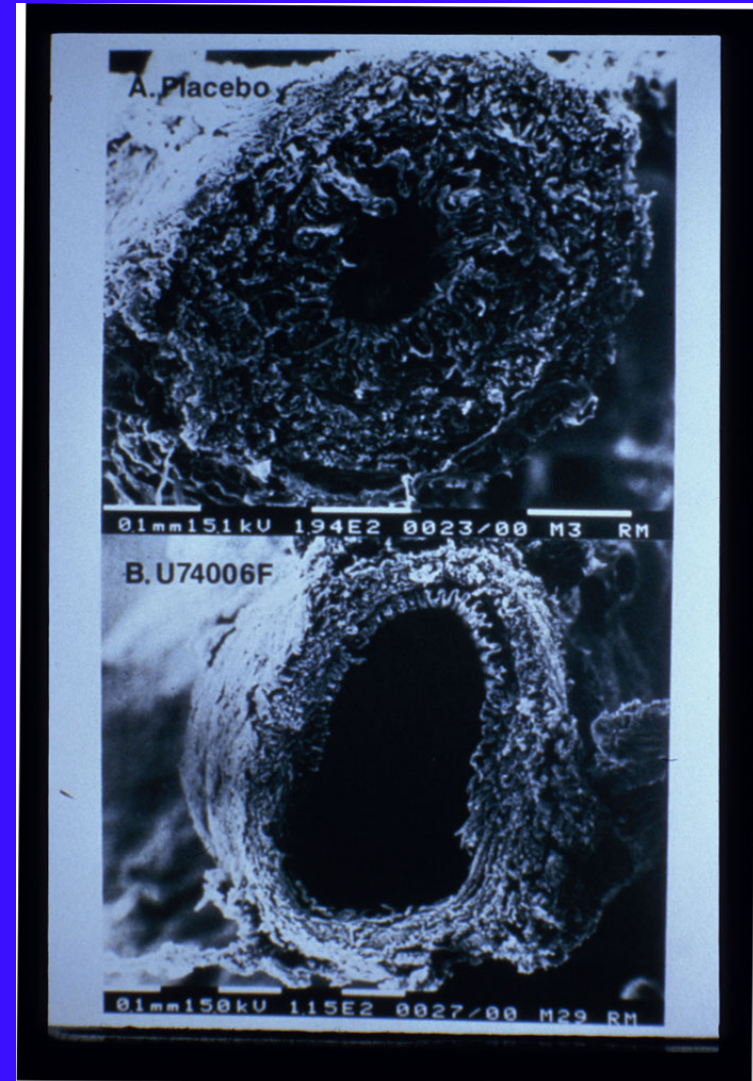
Scanning electron photomicrographs show normal cardiac myocytes (left) and cells after 30-minute treatment with cumene hydroperoxide (right). Note contraction and formation of membrane "blebs" on the cell surface.

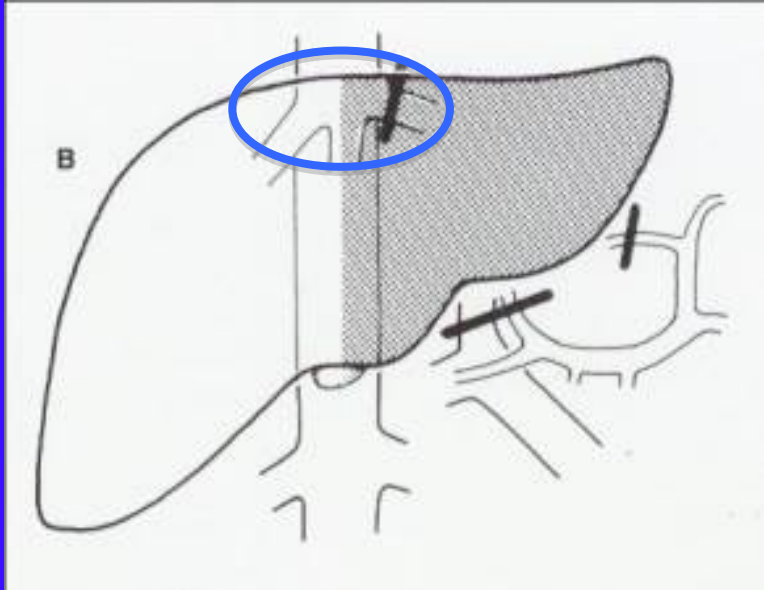
Photomicrographs courtesy of Dr A. A. Noronha-Dutra.

Akutes Nierenversagen (Acute Tubular Necrosis)

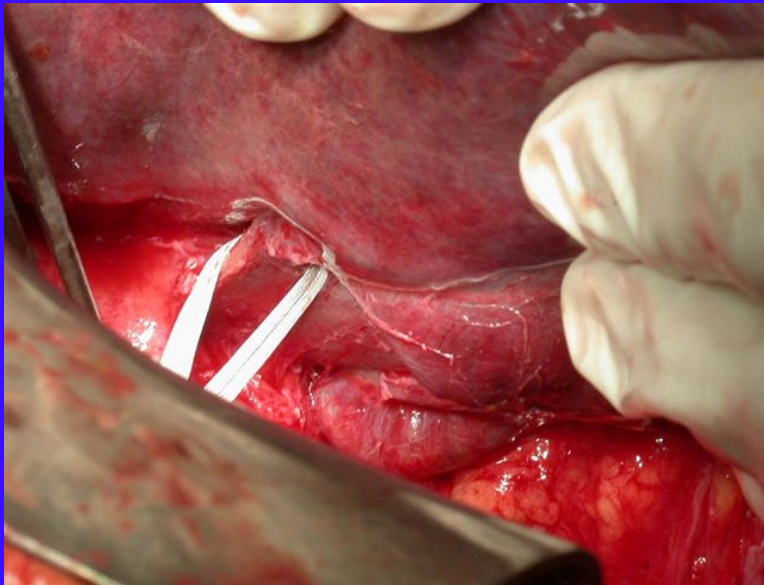


Harnstoff ↑
Crea ↓
GFR ↓





postop.
Leberfunktionsstörungen

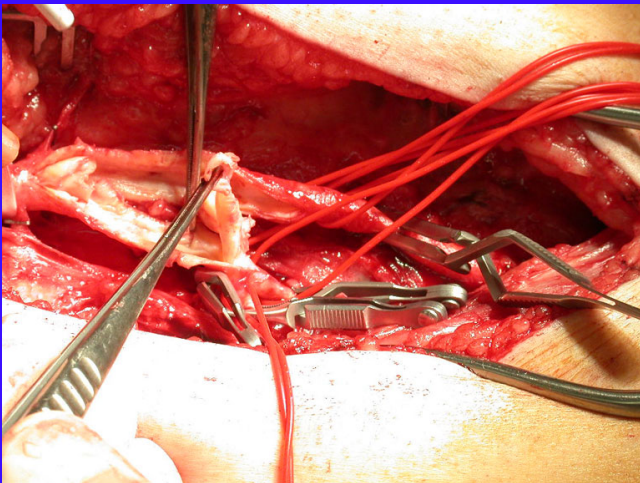
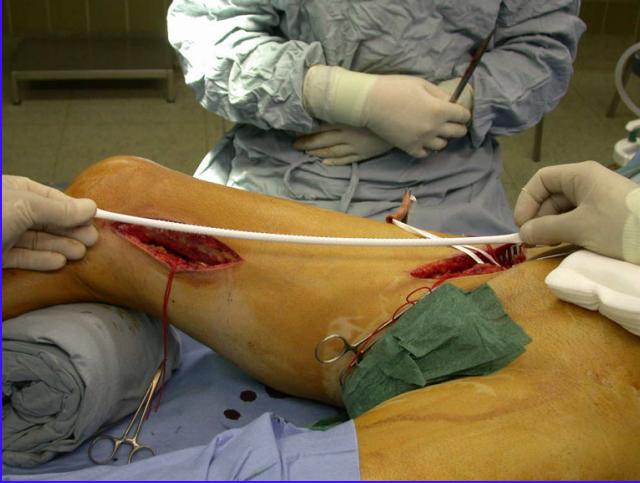


Darmwandödem und Zottennekrosen

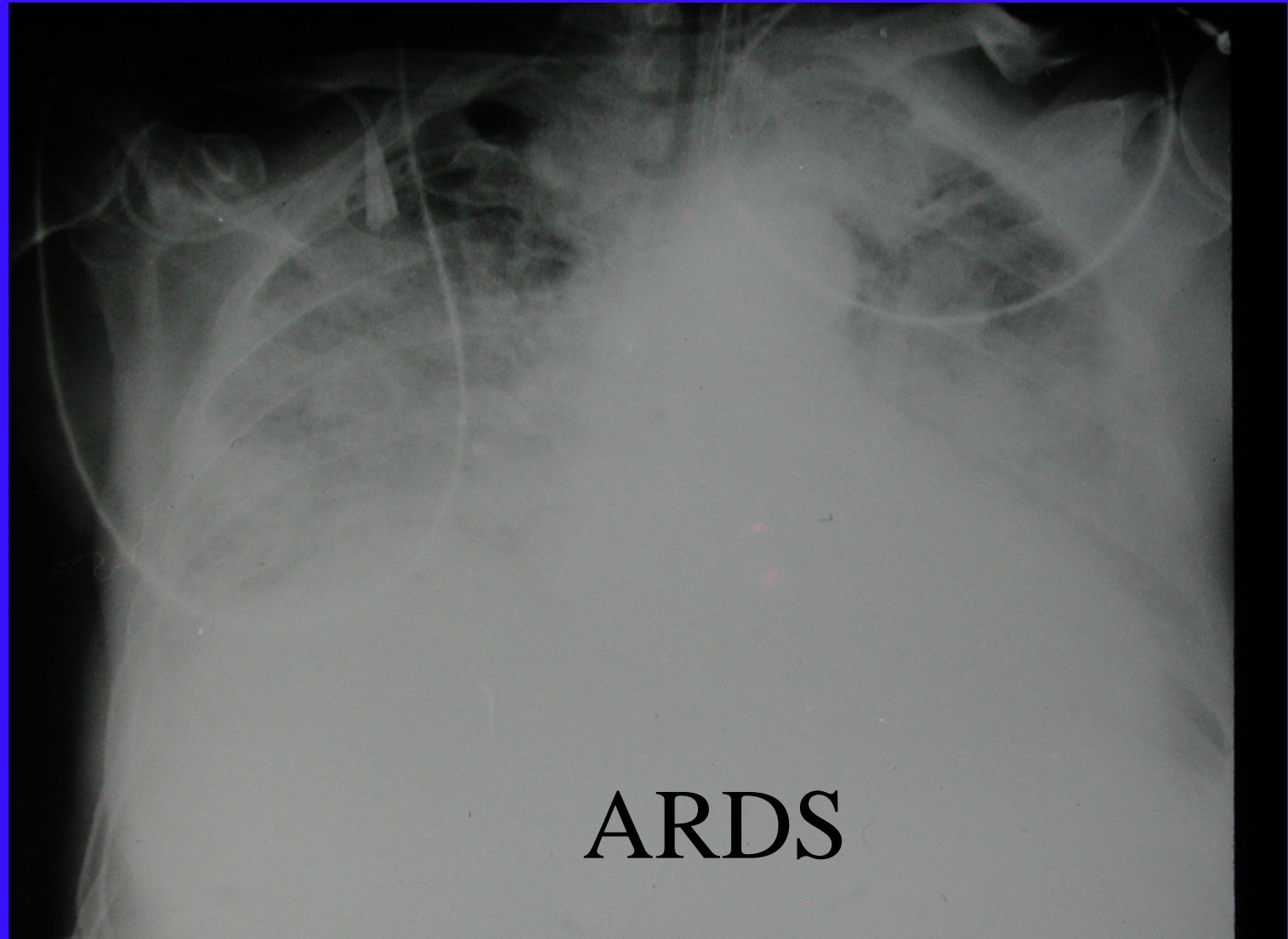


Motilität, Resorption, Translokation

Reperfusionsoedem nach femcruralem Bypass

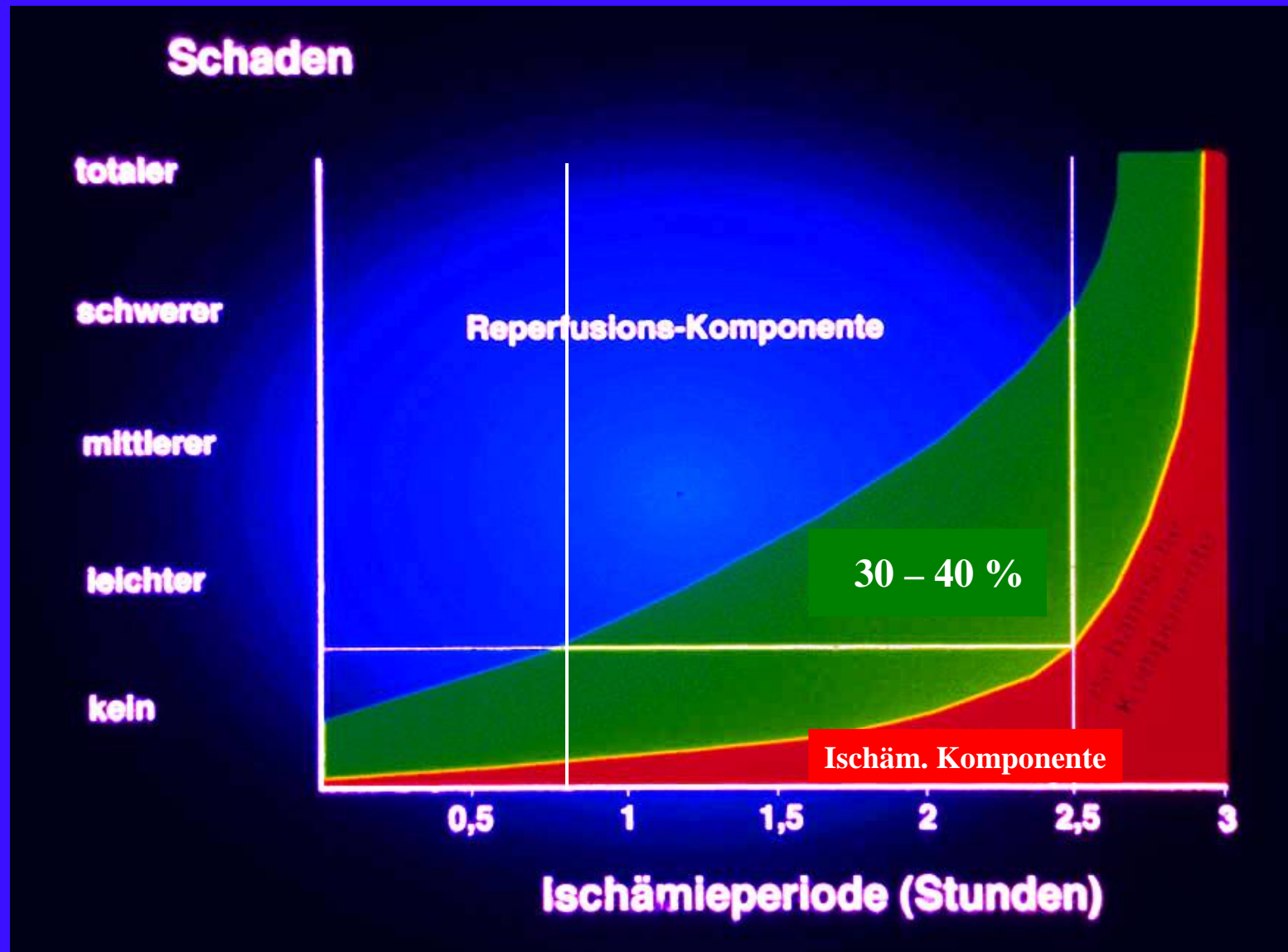


weisse Lunge



ARDS

Ischämie - Reperfusionsschaden



I / Reperfusion

lokale u./od. systemische Entzündungsreaktion

SIRS (systemic inflammatory response syndrome)

MODS (multi organ dysfunction syndrome)

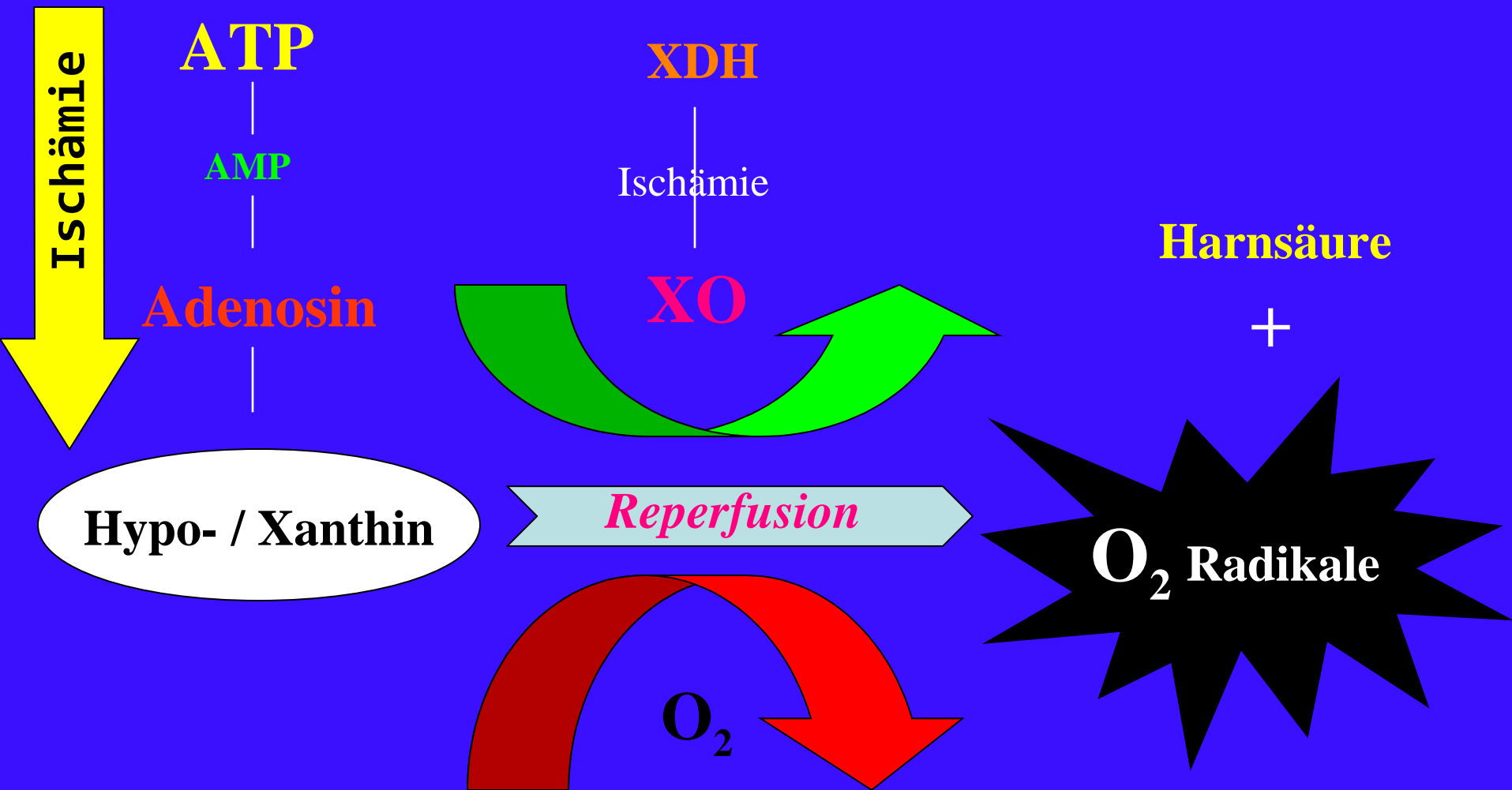
Organschaden / DEATH

MODS

Mortalität :	1 Organ	40%
	2 Organe	60%
	3 Organe	100%

SIRS

Biochemische Grundlagen



radicals

O_2^\bullet Superoxid

H_2O_2 Hydroperoxyl

OH^\bullet Hydroxyl

^1O Singulet – O

OONO^\bullet Peroxinitrit



Lipidperoxidation

Complement
C5

Makrophagen
PMN's

Radikale

Apoptose

Thrombozyten

PLA₂

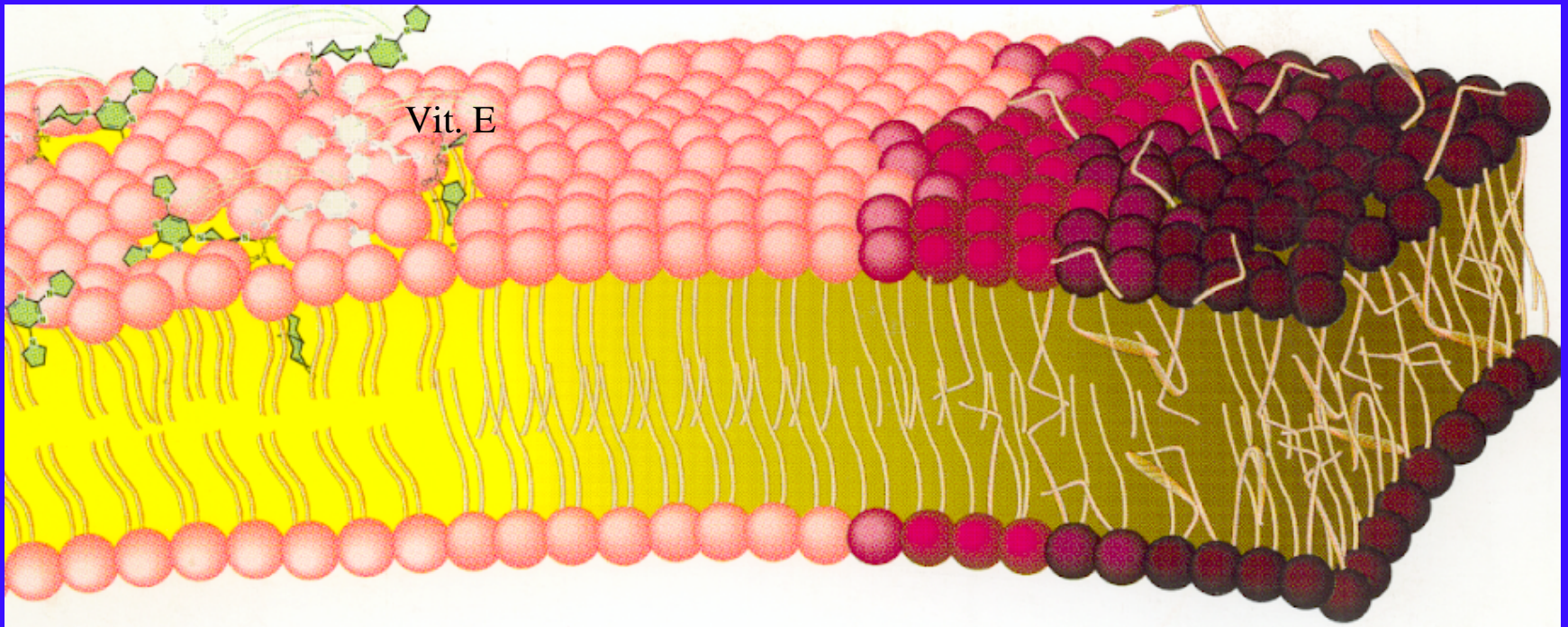
Oxygenasen

Lip - Cyclo - Mono -

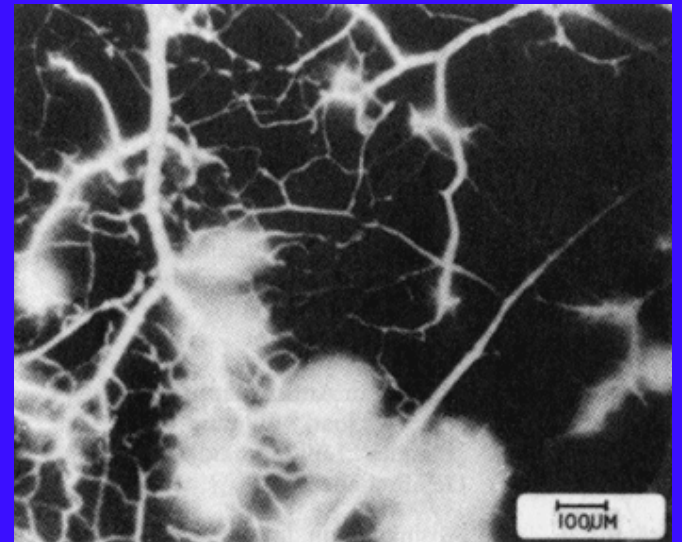
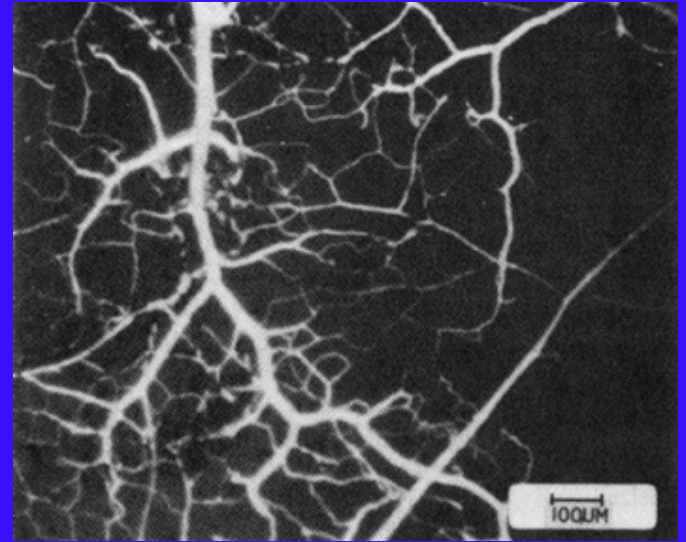
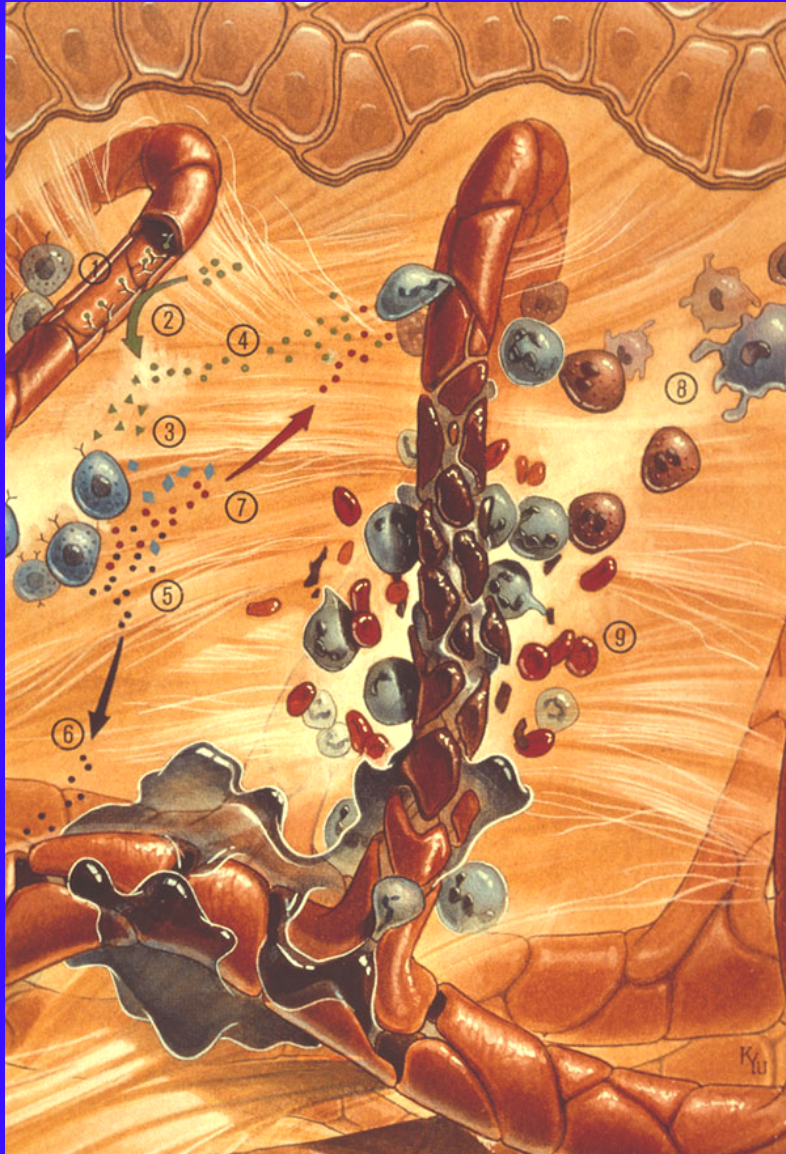
Arachidonsäure

Endothel

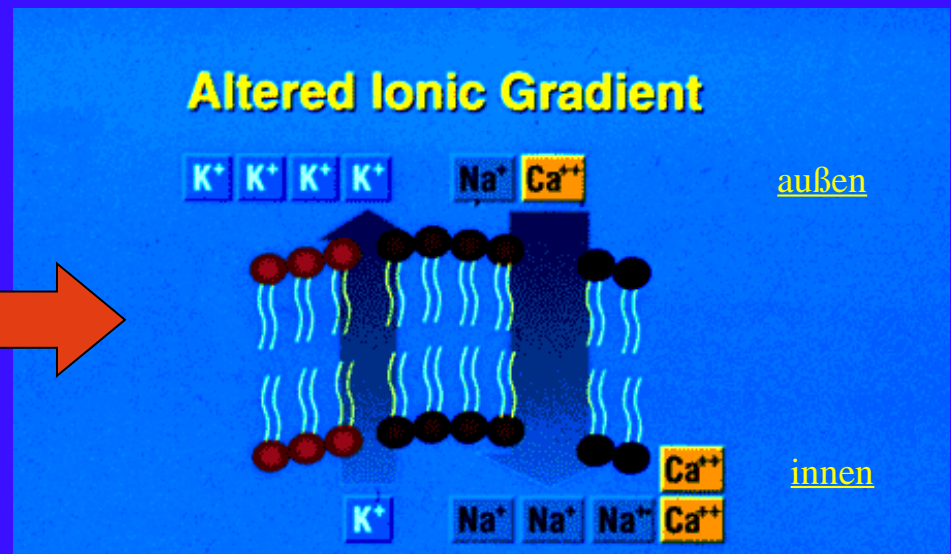
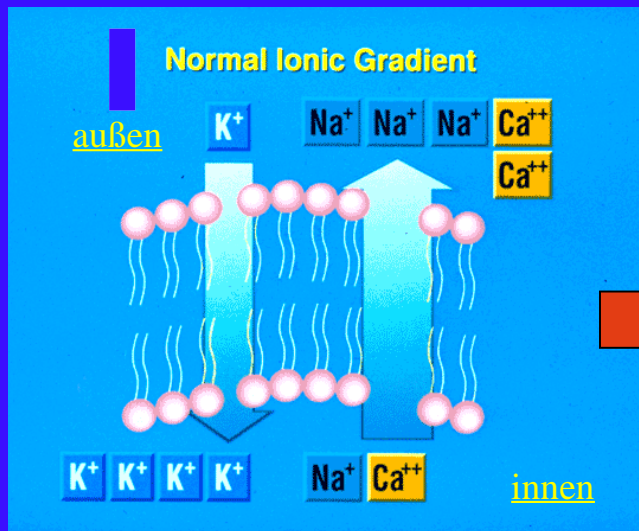
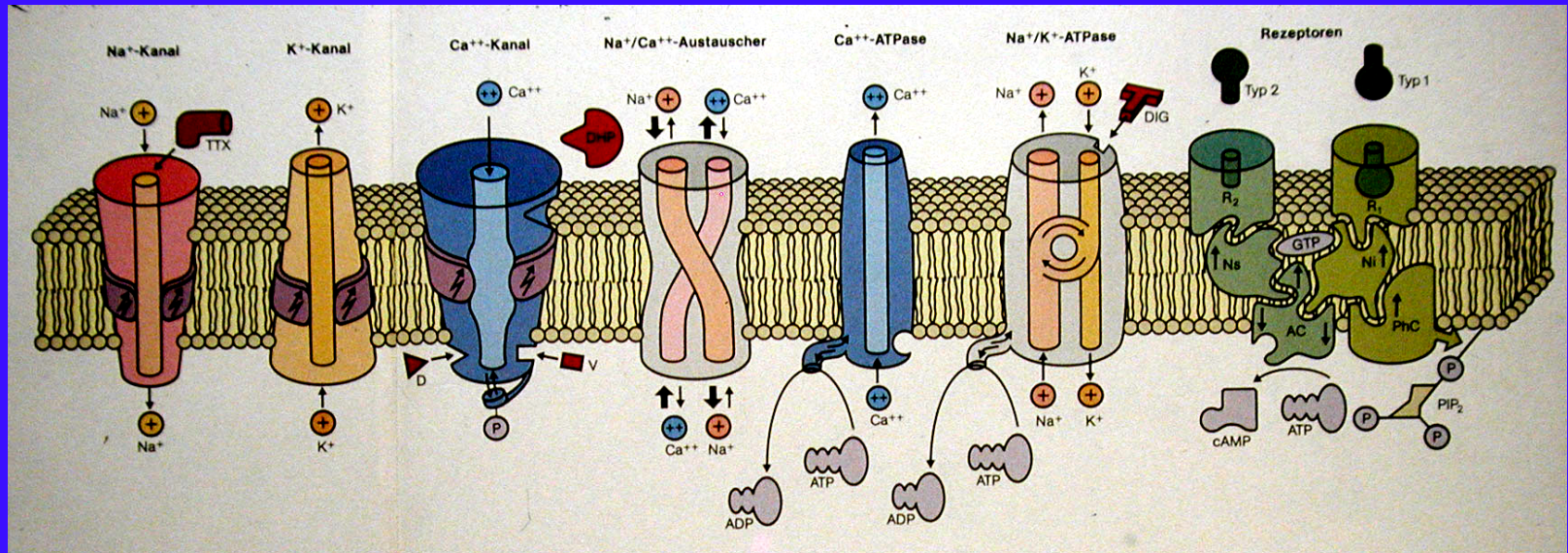
Lipidperoxidation



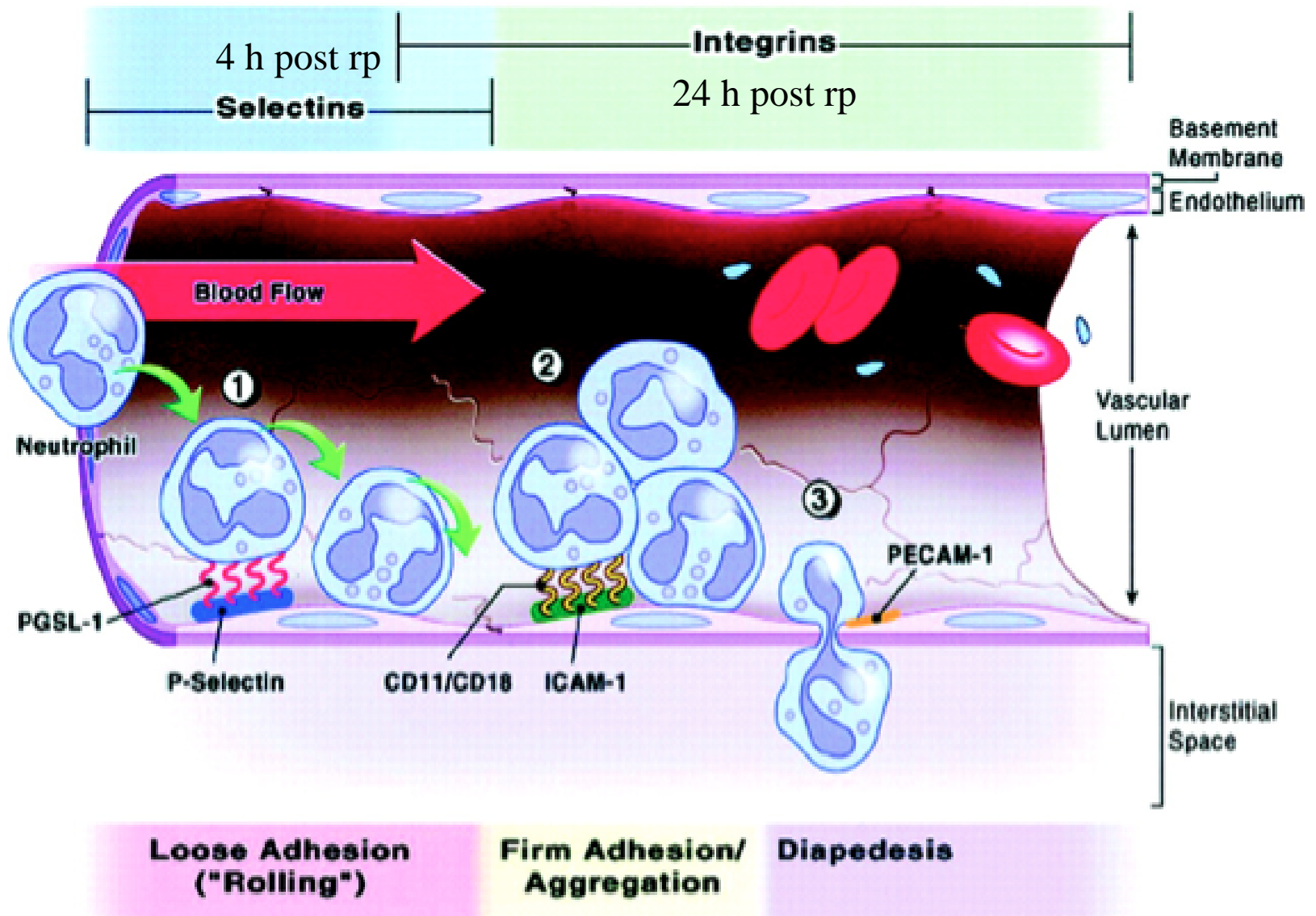
Vit. E : Phospholipiden = 1 : 10 - 14



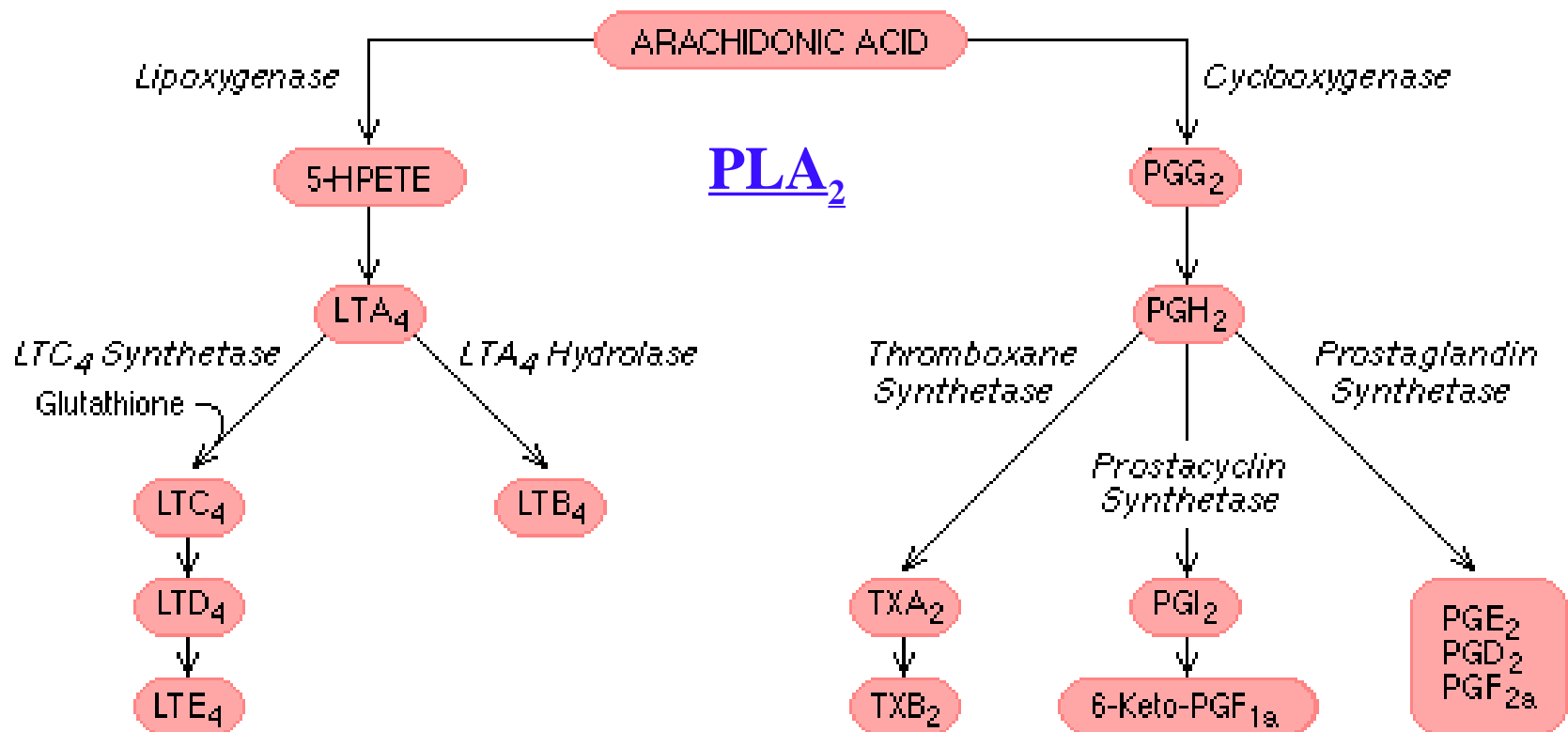
Ionenkanalintegration



I-R-induced leucocyte-endothelial cell adherence and transmigration.

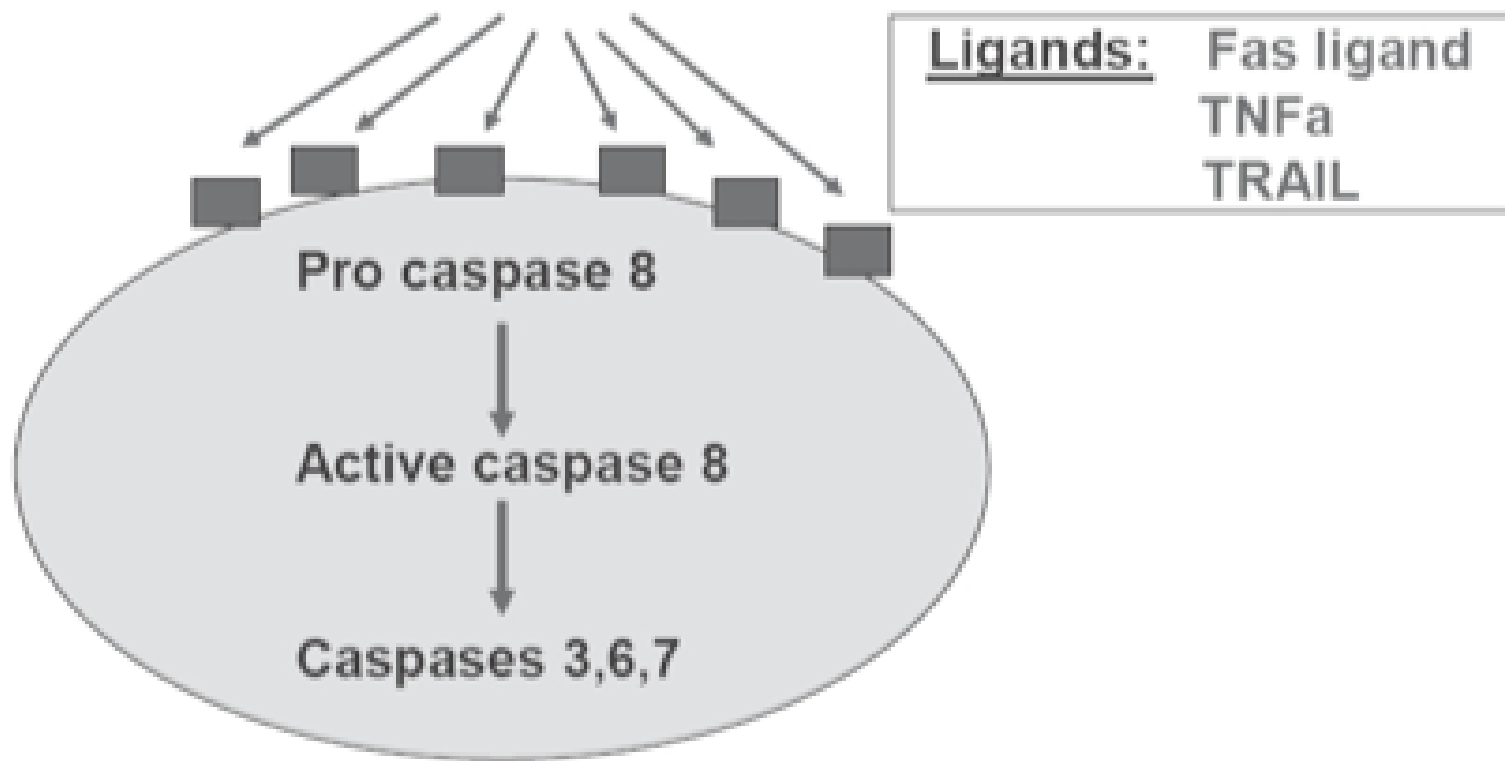


Arachidonsäurekaskade

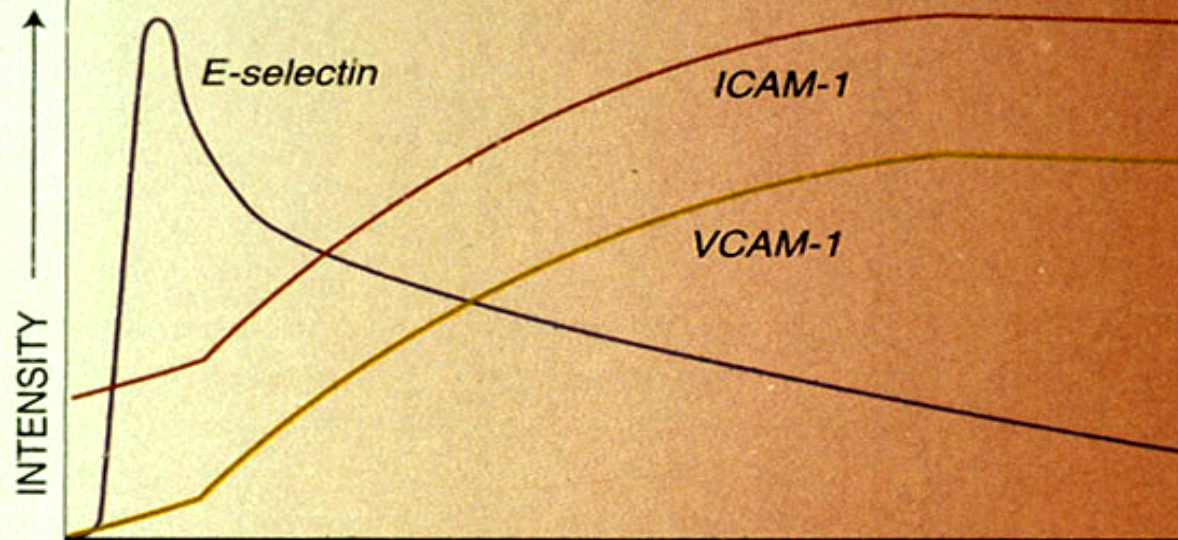


Apoptose

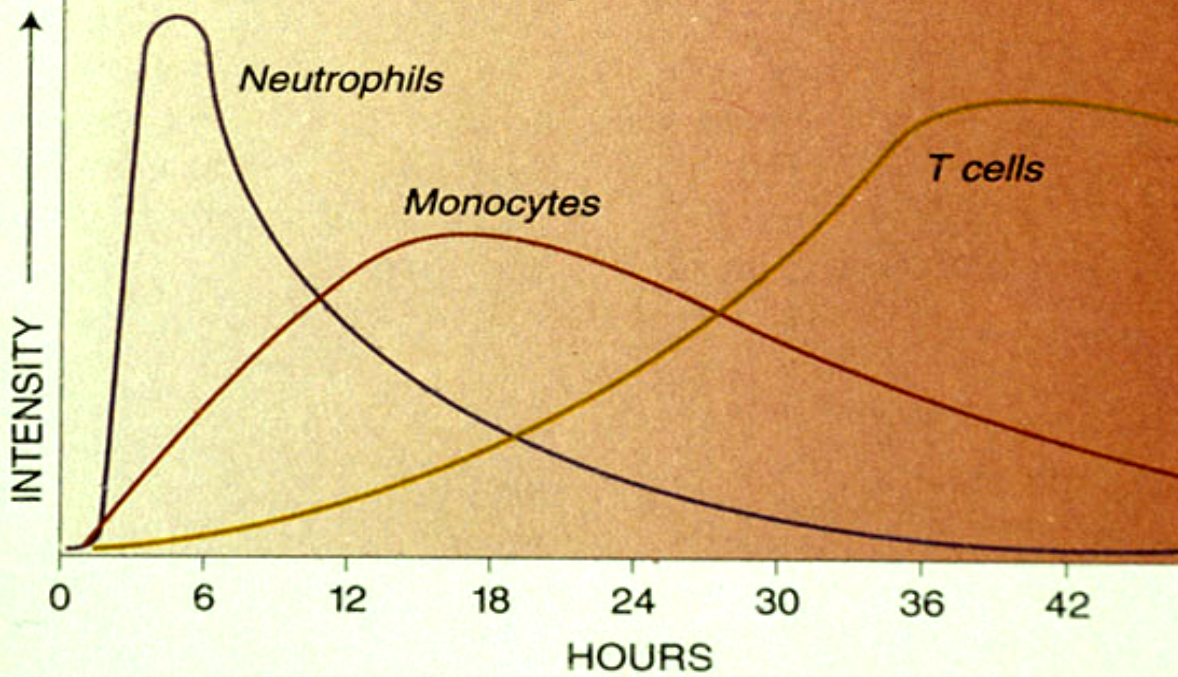
Death Receptors: Fas, TNFR1, DR 3-6



Endothelial Adhesion Molecule Expression



Leukocyte Infiltration



Kaskade

Radikale

zeitabhängig

Lipidperoxidation

PMN - Endothelaktivierung

Arachidonsäureaktivierung

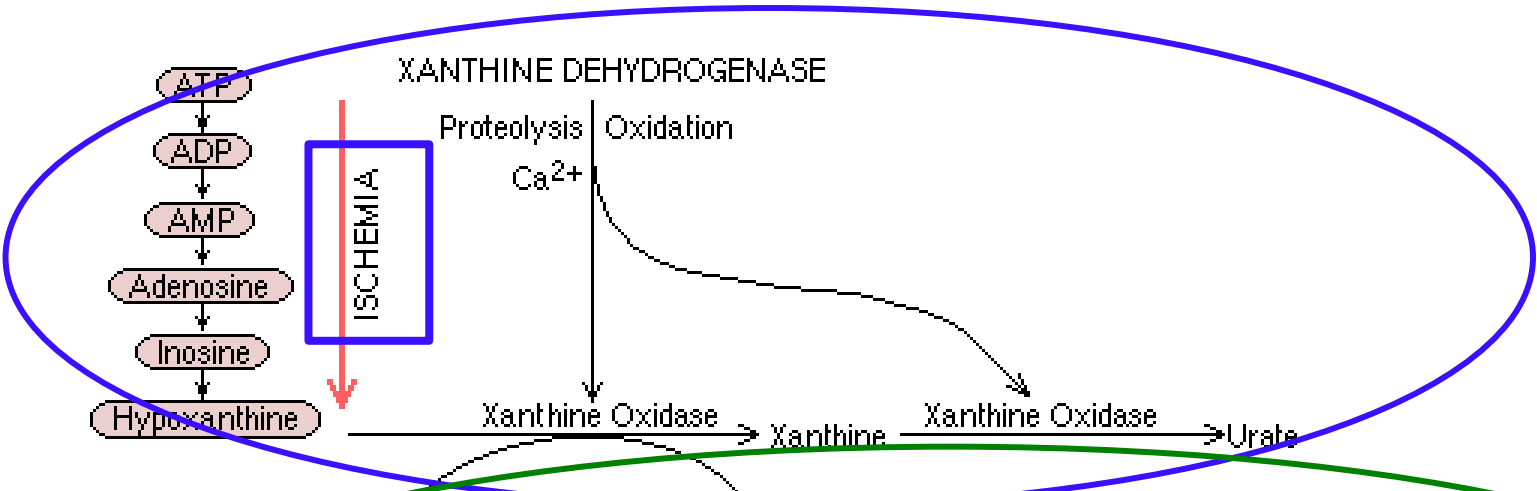
Entzündungsmediatoren

Reperfusion-SCHADEN

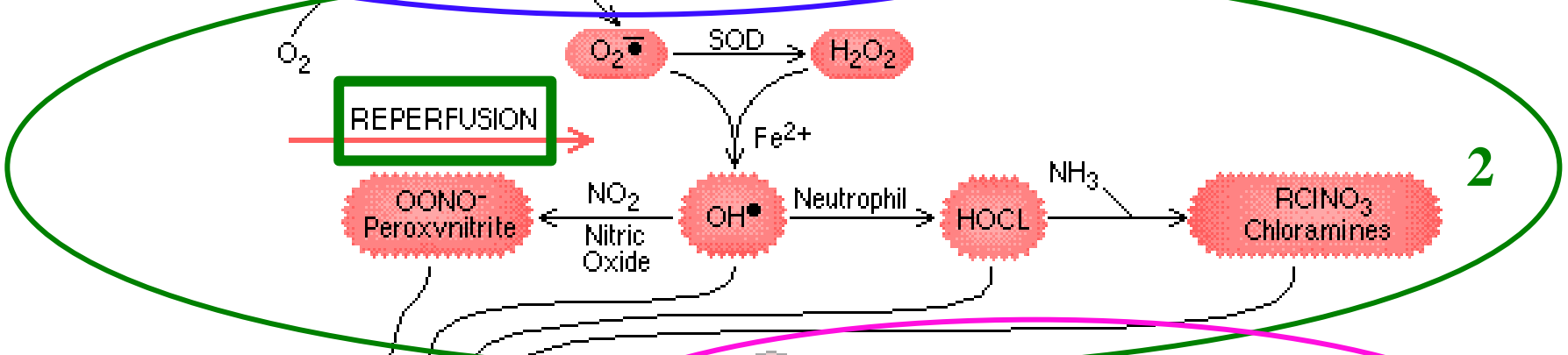
Reperusionsparadoxon

Stadien

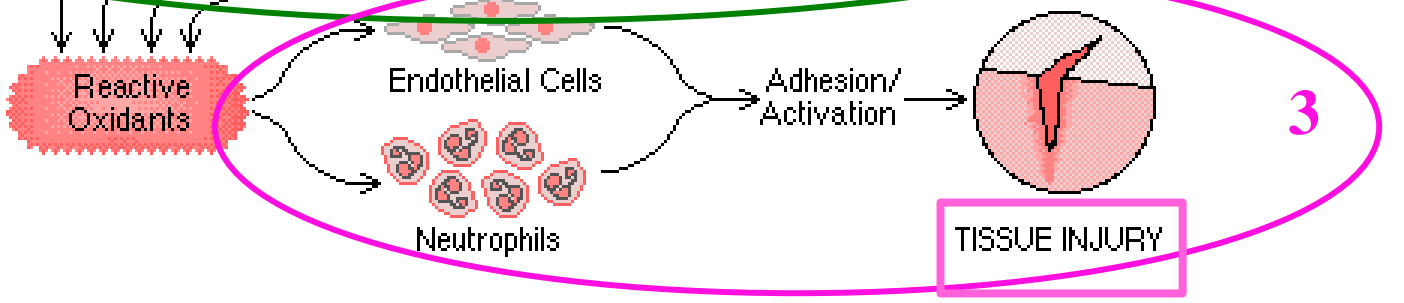
1



2



3



Physiologische **Antioxidantien**

Enzyme
intrazellulär

SOD
Katalase
GSH

Chain breaking

Extrazellulär

Ascorbinsäure

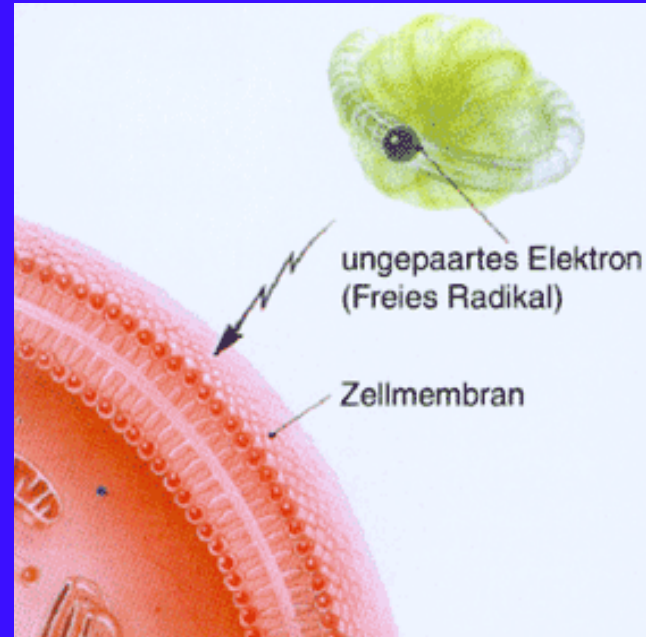
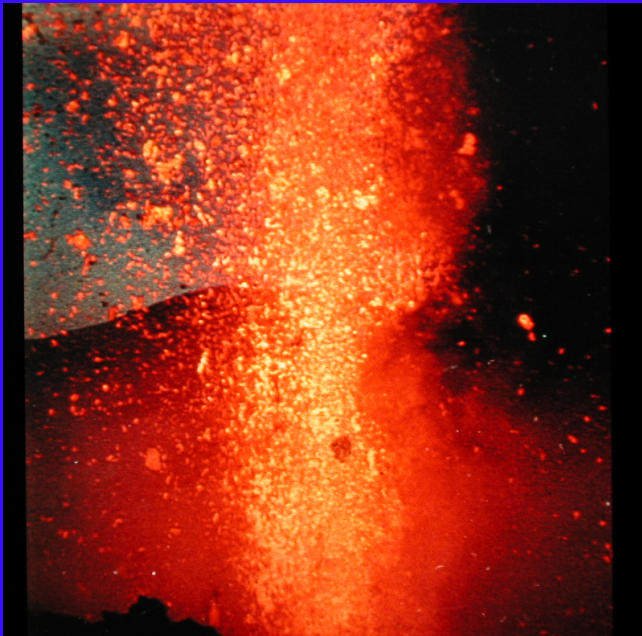
Urate
SH-Gruppen
Bilirubin

Tocopherole

Carotinoide

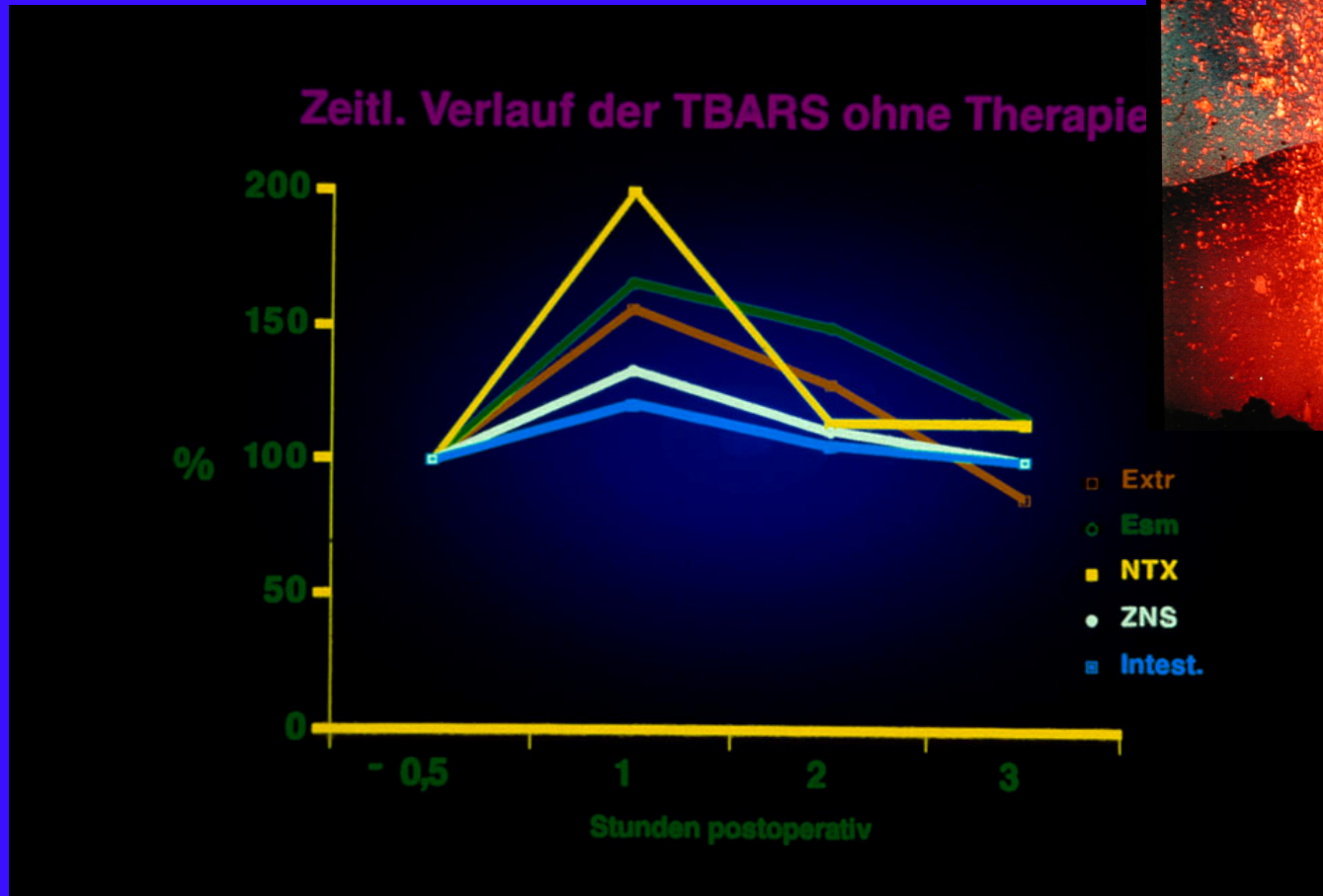
Preventive Antioxidants

Transferrin
Coeruloplasmin
Haptoglobin



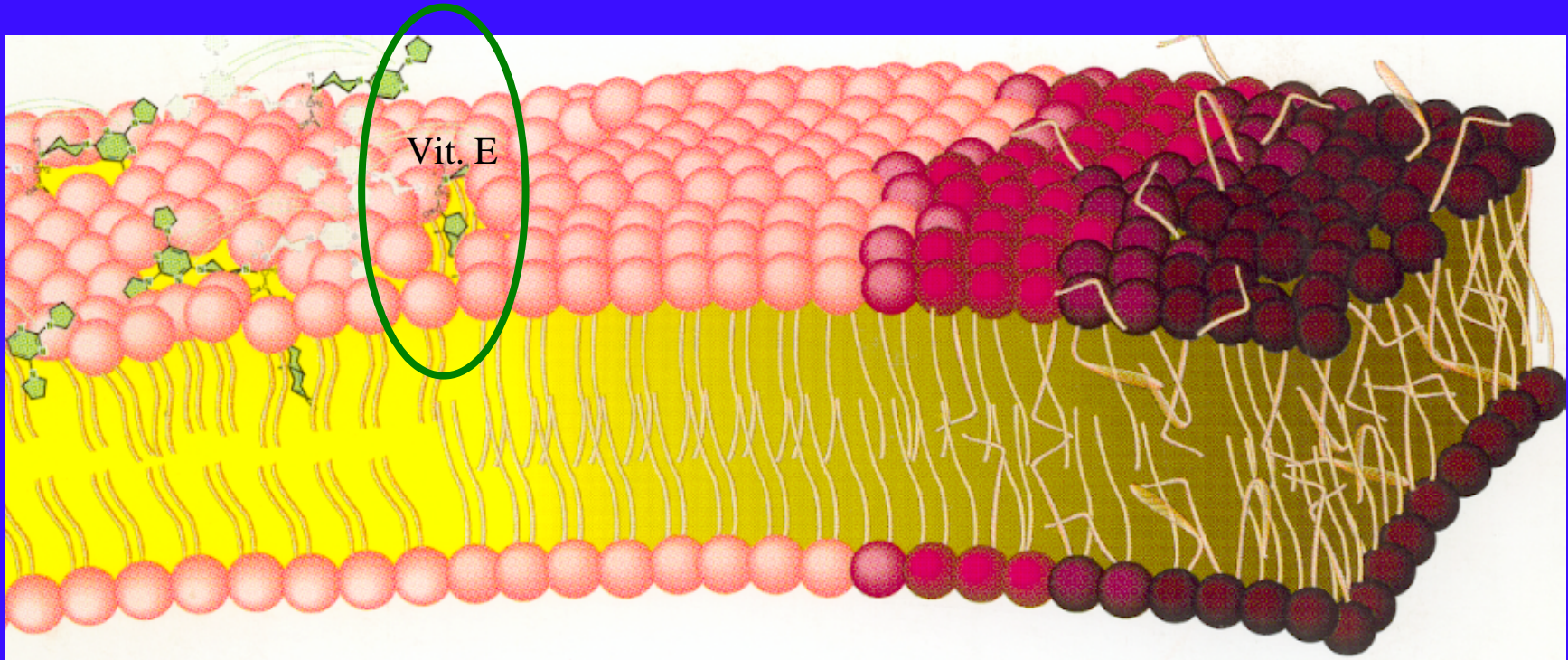
Zu welchem Zeitpunkt
des I / R – Vorganges
werden Radikale freigesetzt ??

Zeitl. Verlauf der TBARS

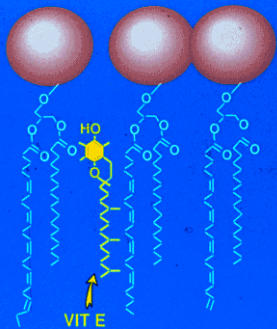


Rabl H. et al., Human plasma lipid peroxide levels show a strong transient increase after successful revascularization operations. Free Rad Biol Med 13 (1992) 281-288

Schutz vor Lipidperoxidation



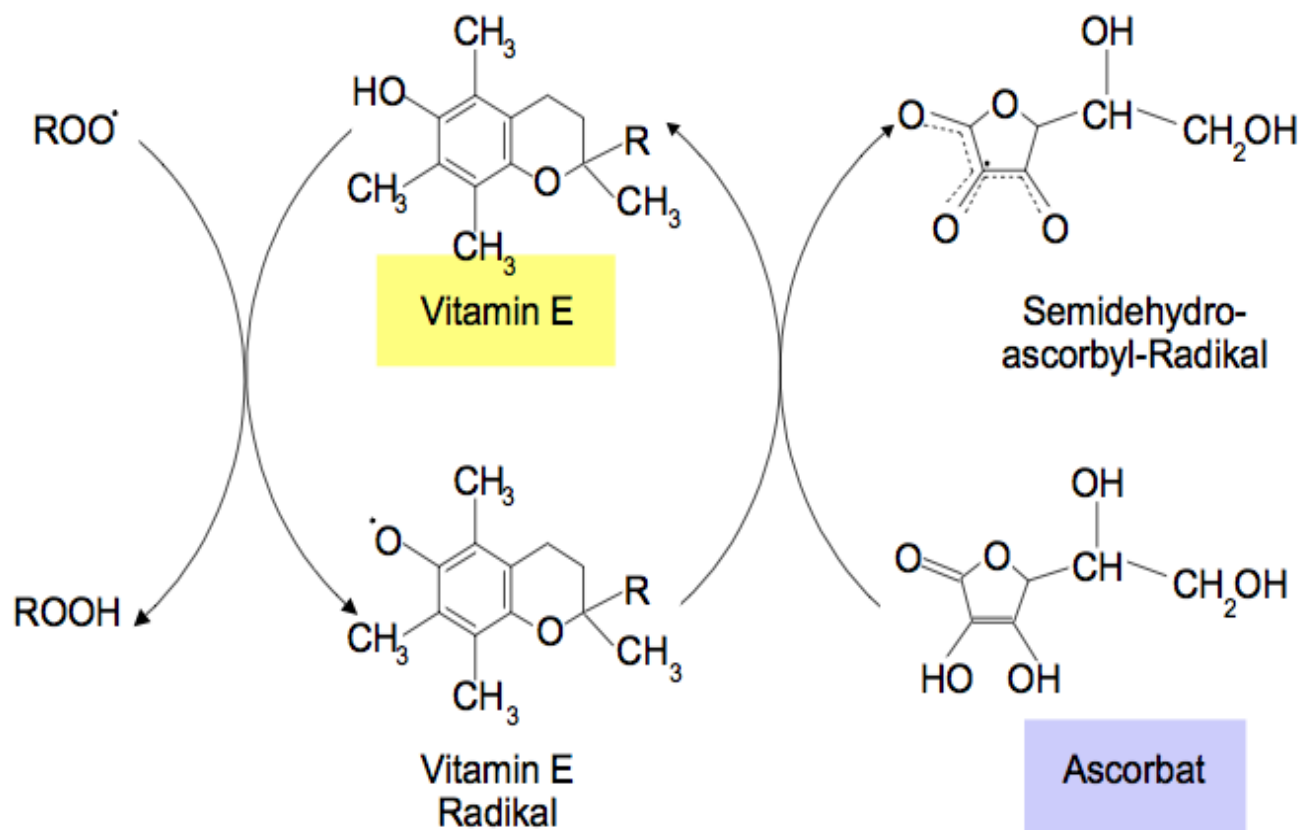
Vitamin E Membrane Stabilization



Vit. E : Phospholipiden = 1 : 10 - 14

L. Parker: Vit. E is nature's master antioxidant

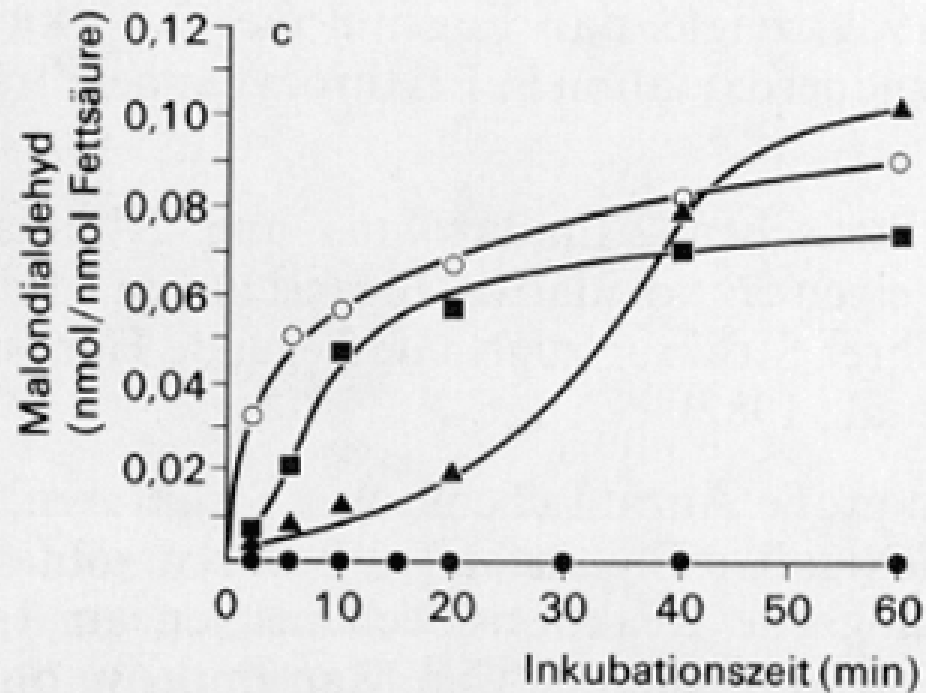
Interaktion Vitamin E und Vitamin C



Recycling des lipidlöslichen Vitamin E durch das wasserlösliche Vitamin C

Vit E / C

- Liposomen allein (Kontrolle)
- ▲—▲ + 100 μ M Ascorbat
- 10 μ g Vit. E
- 10 μ g Vit. E + 100 μ M Ascorbat



Antioxidantiencocktail

1 ampoule = 10 ml

5,5 mg retinol palmitate

500,0 mg ascorbate

5,0 mg alpha tocopherol acetat

1,0 mg DL - alpha tocopherol

50,0 mg thiaminchloride - hydrochloride

10,0 mg riboflavin 5 phosphate sodium

100,0 mg nicotinamide

25,0 mg dexpanthenol

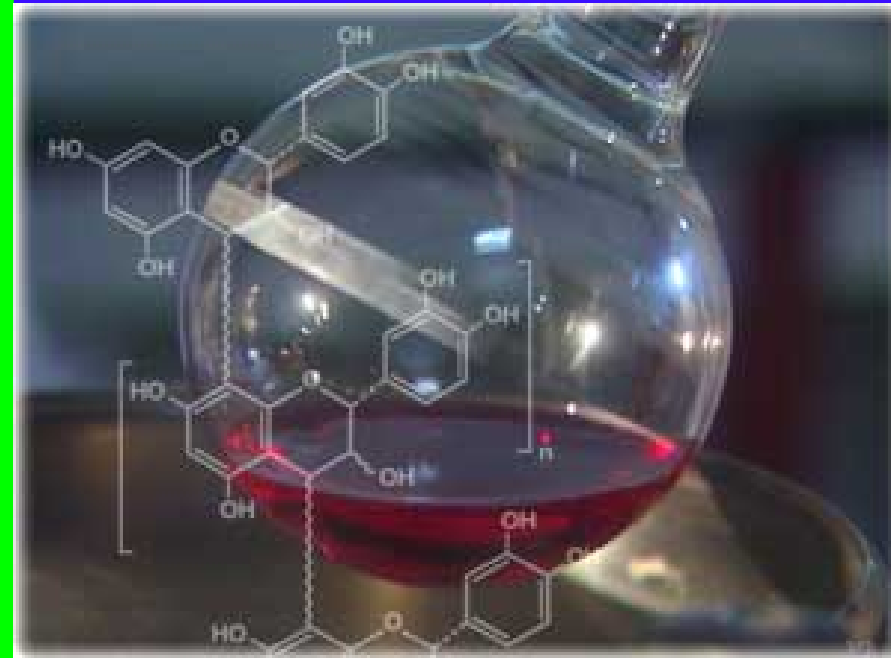
150 mg benzylalcohol

500,0 mg polysorbate 80

200,0 mg propylenglycol

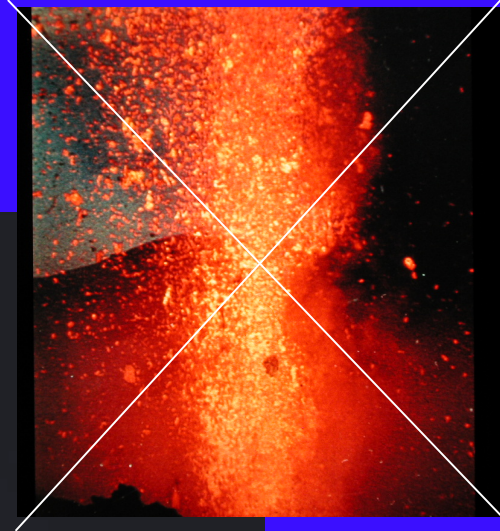
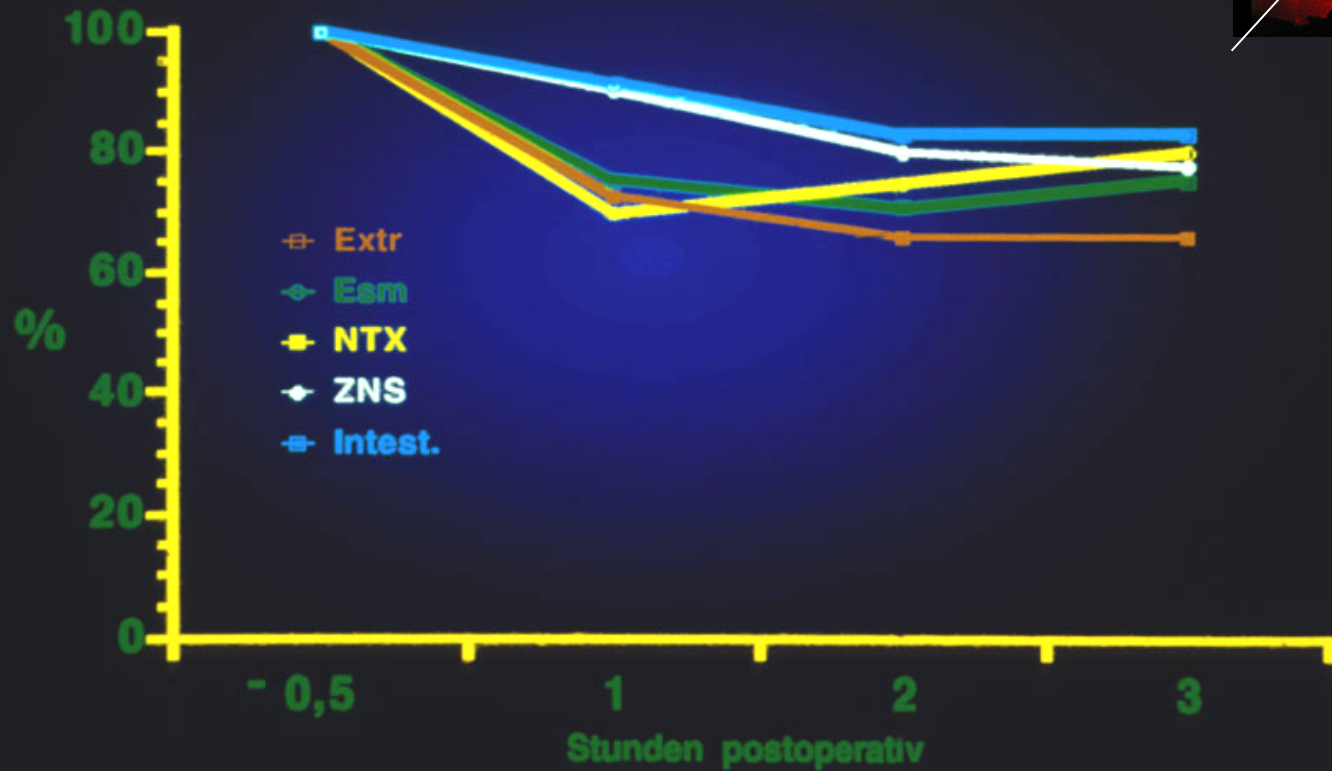
2500,0 mg glycerin 85%

360,0 mg trometamol

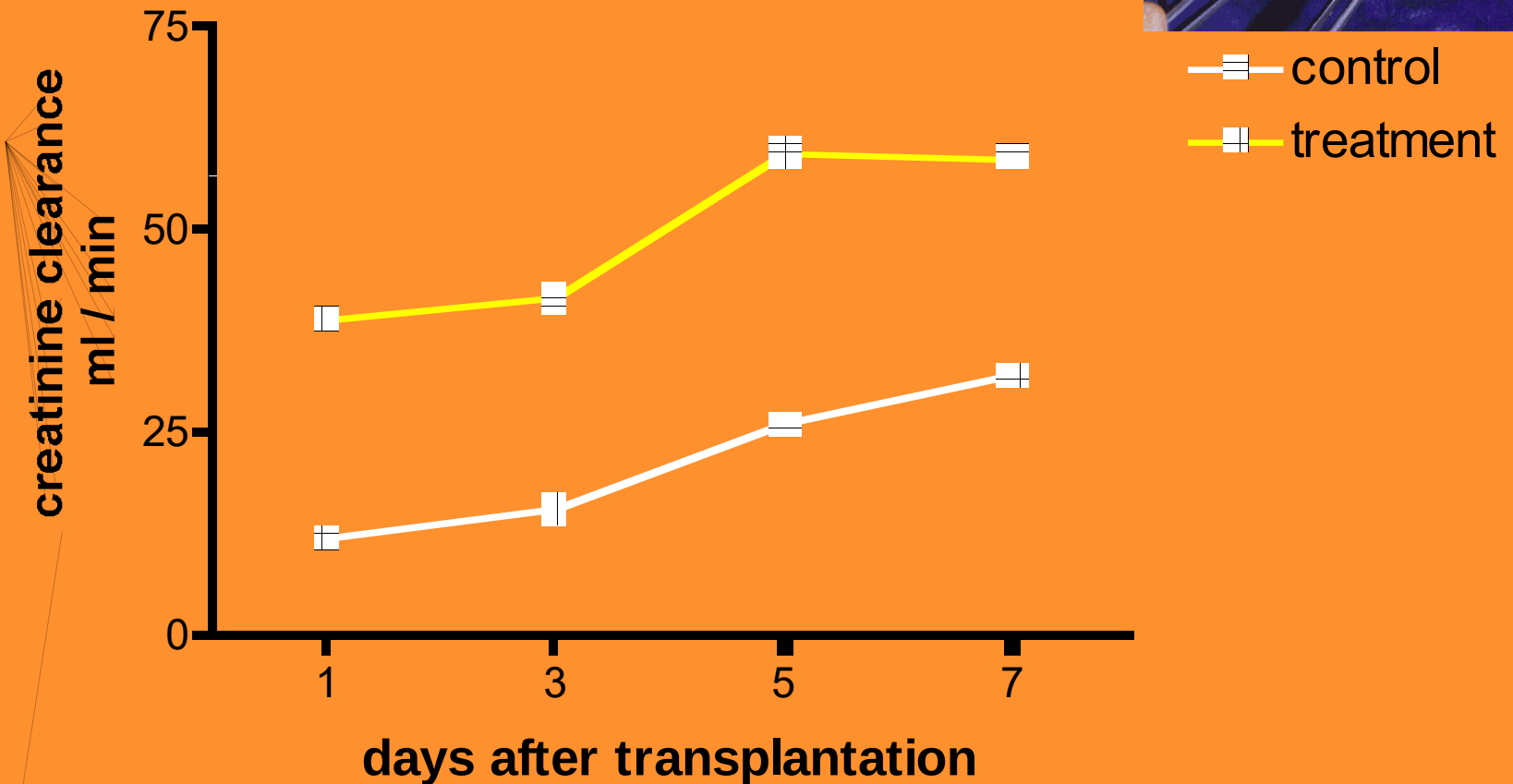
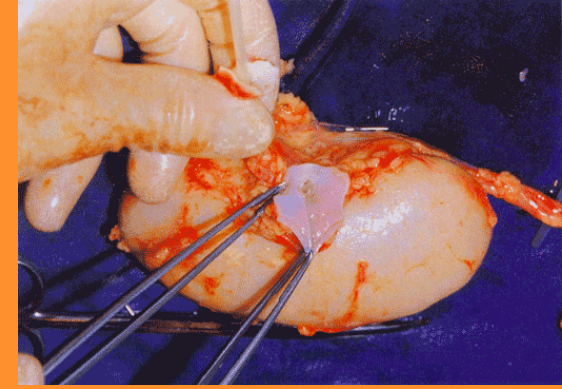


vitamin cocktail
Omnibionta*

Zeitl. Verlauf der TBARS mit Therapie



kidney transplantation



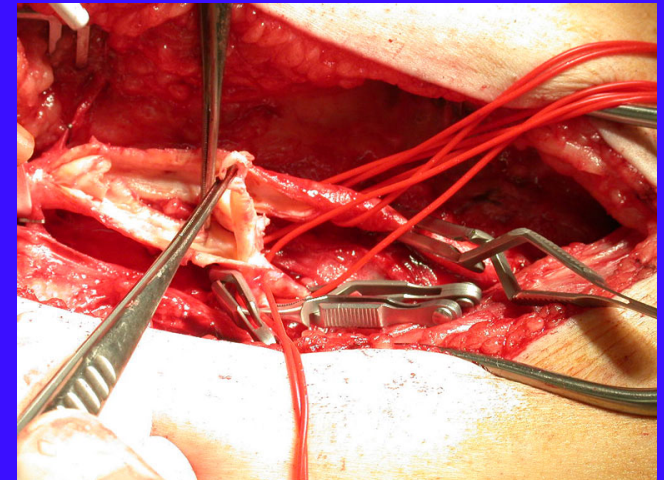
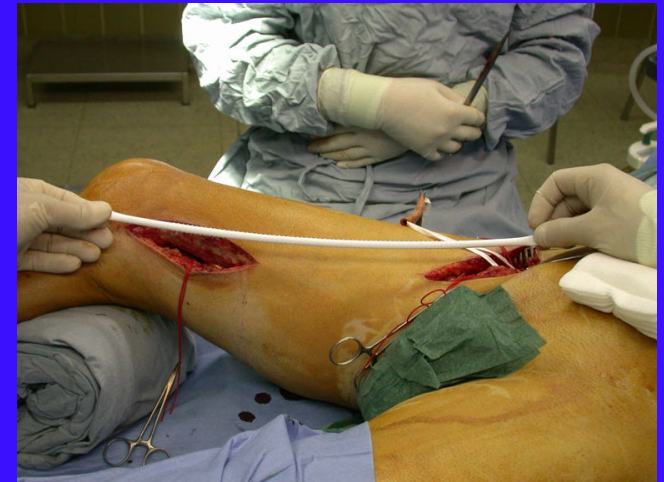
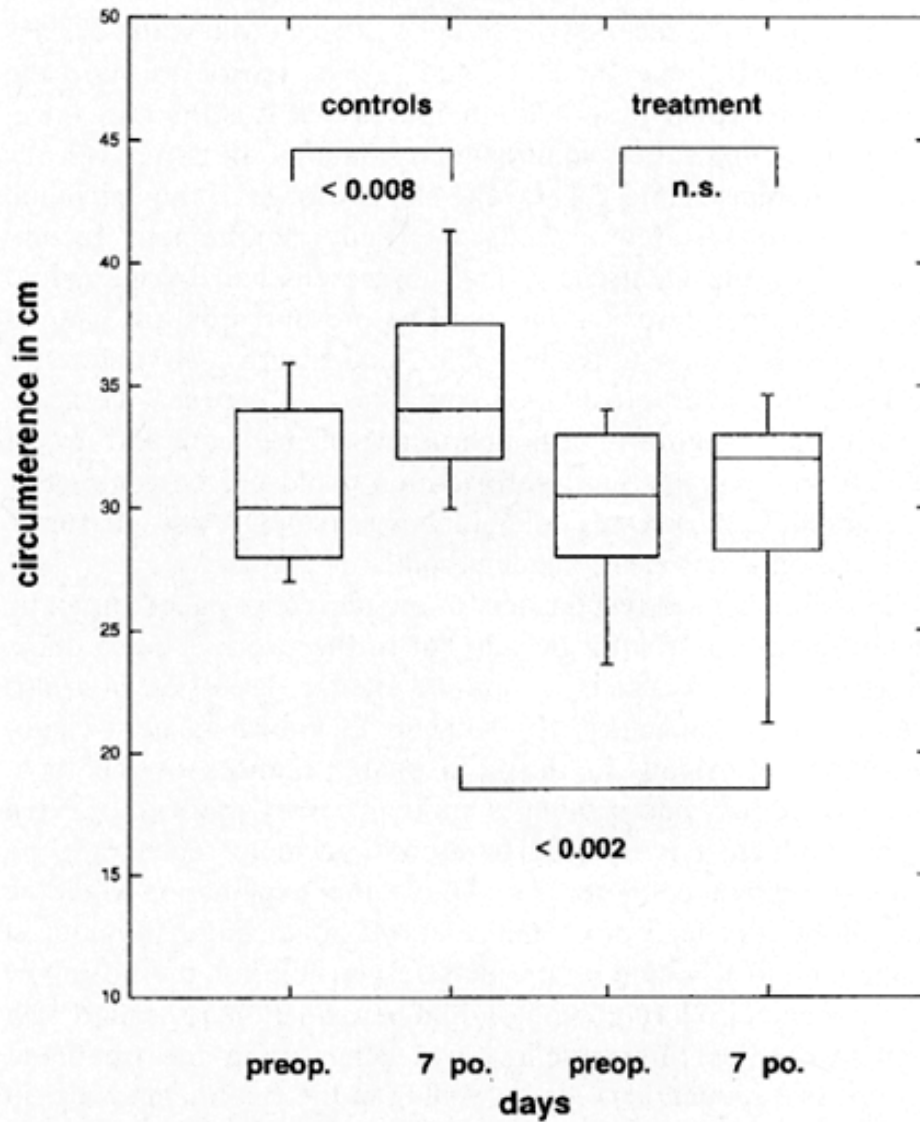
Rabl H et al., A multivitamin infusion prevents lipid peroxidation
And improves transplantation performance. **Kidney Int. 43 (1993) 912 -917**

Rationale for the use of antioxidant vitamins in clinical organ transplantation

In 1992, **Rabl H.** and co-workers were the first
to take these findings into the clinic.

K. Messmer, HA. Lehr. Transplantation 1996; Vol. 62, 1197 - 1199

Beinumfangsdifferenz



Rabl H. et al.: Antioxidative vitamin treatment: Effect on lipid peroxidation and limb swelling after revascularization operations. World J Surg 19, 738-744; 1995

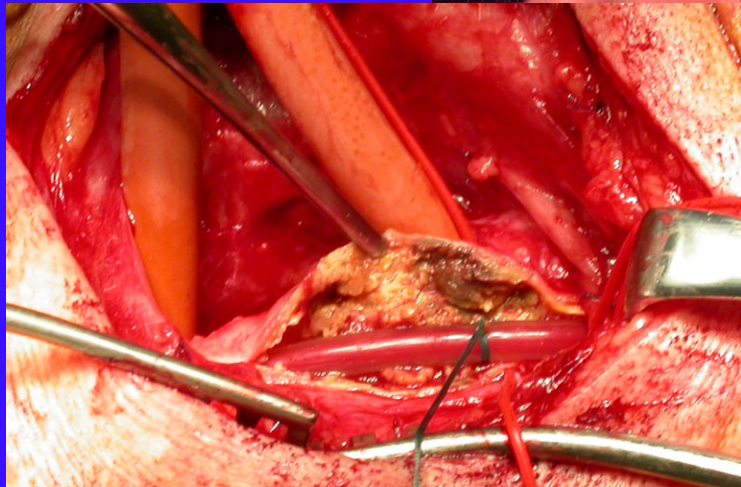
Skelettmuskelveränderungen

Neumayer C., Huk et al., A-tocopherol pretreatment reduces ischemia reperfusion injury in rabbit skeletal muscle.

European Surgery - Acta Chirurgica Austriaca 34; 90-94, 2002



Hypertonus
Cephalea



Rabl H. et al. Diminished production of malondialdehyde after carotid artery surgery as a result of vitamin administration. Med. Sci. Res. 1996; 24: 777- 80

vitamin cocktail
Omnibionta*

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1,0 mg DL - alpha tocopherol

50,0 mg thiaminchloride - hydrochloride

10,0 mg riboflavin 5 phosphate sodium

100,0 mg nicotinamide

25,0 mg dexpanthenol

150 mg benzylalcohol

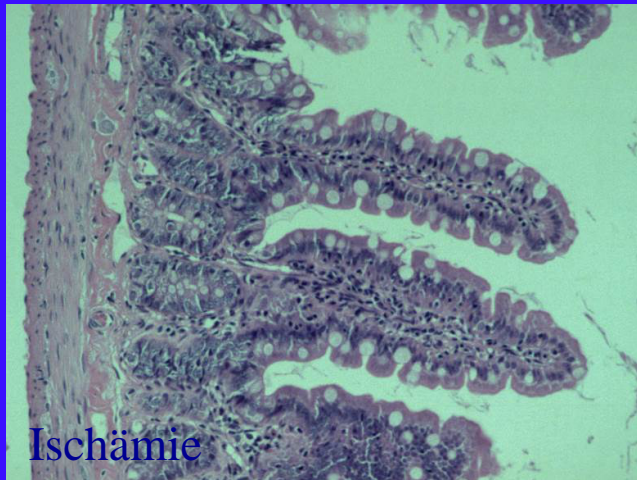
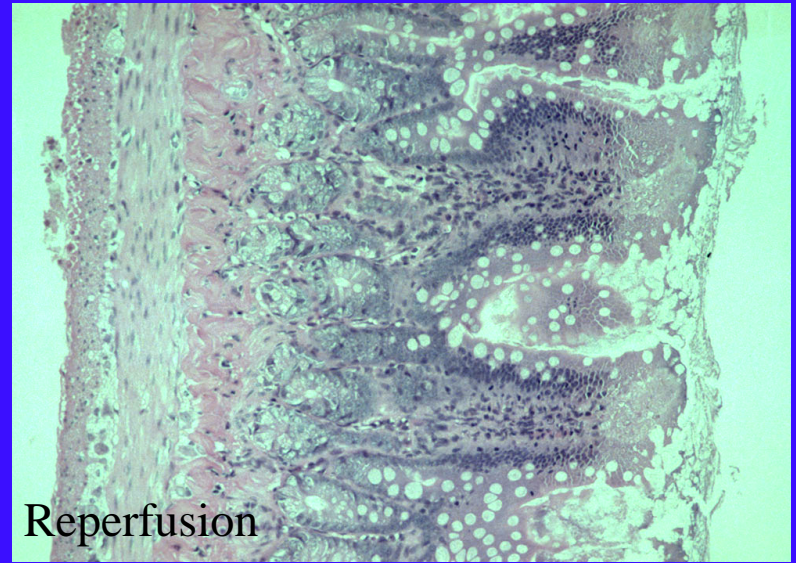
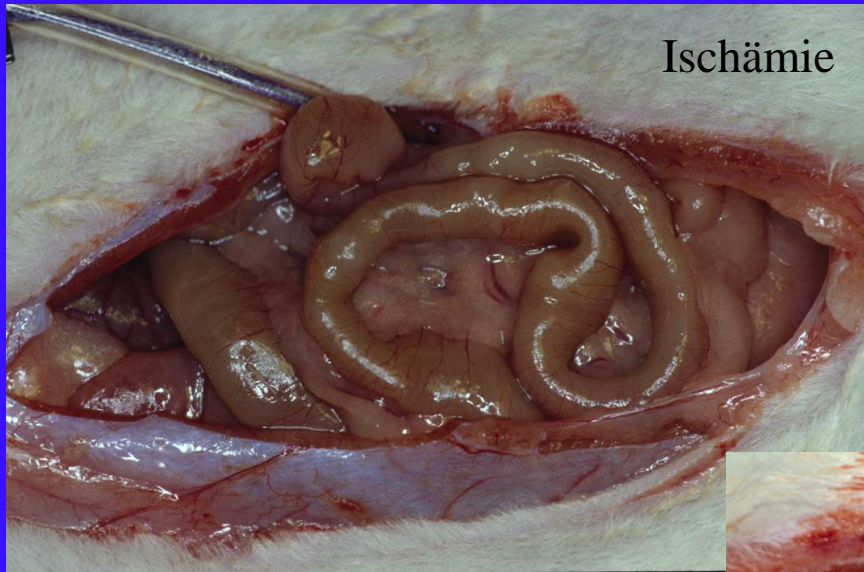
500,0 mg polysorbate 80

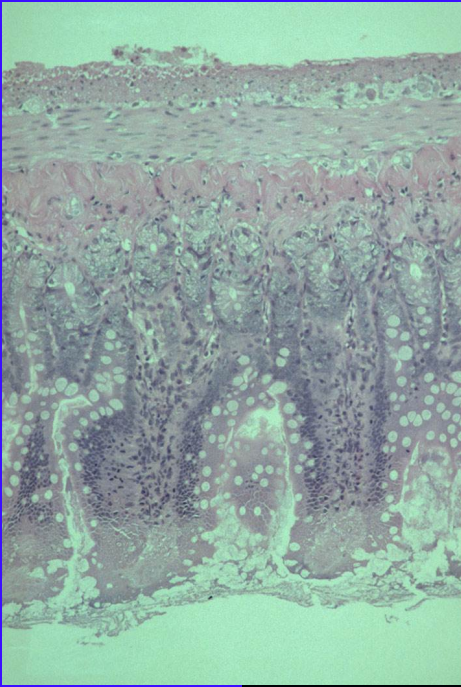
200,0 mg propylenglycol

2500,0 mg glycerin 85%

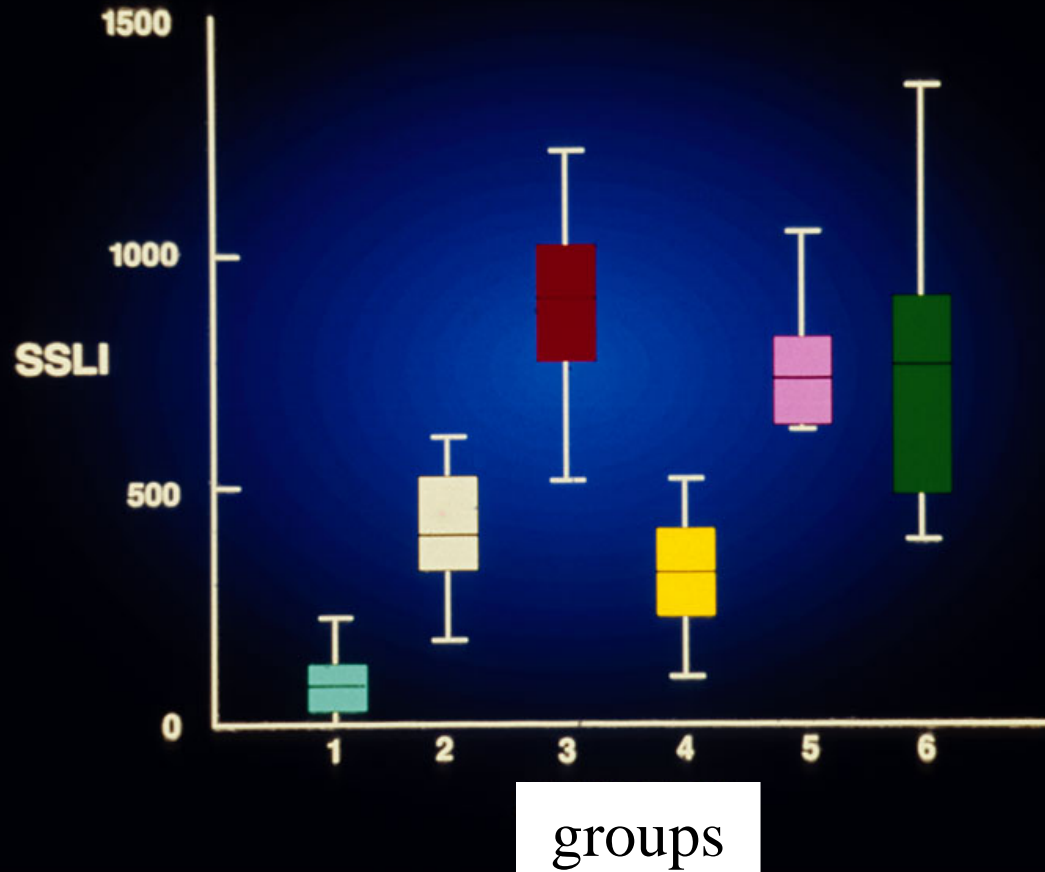
360,0 mg trometamol

Intestinale Ischämie / Reperfusion



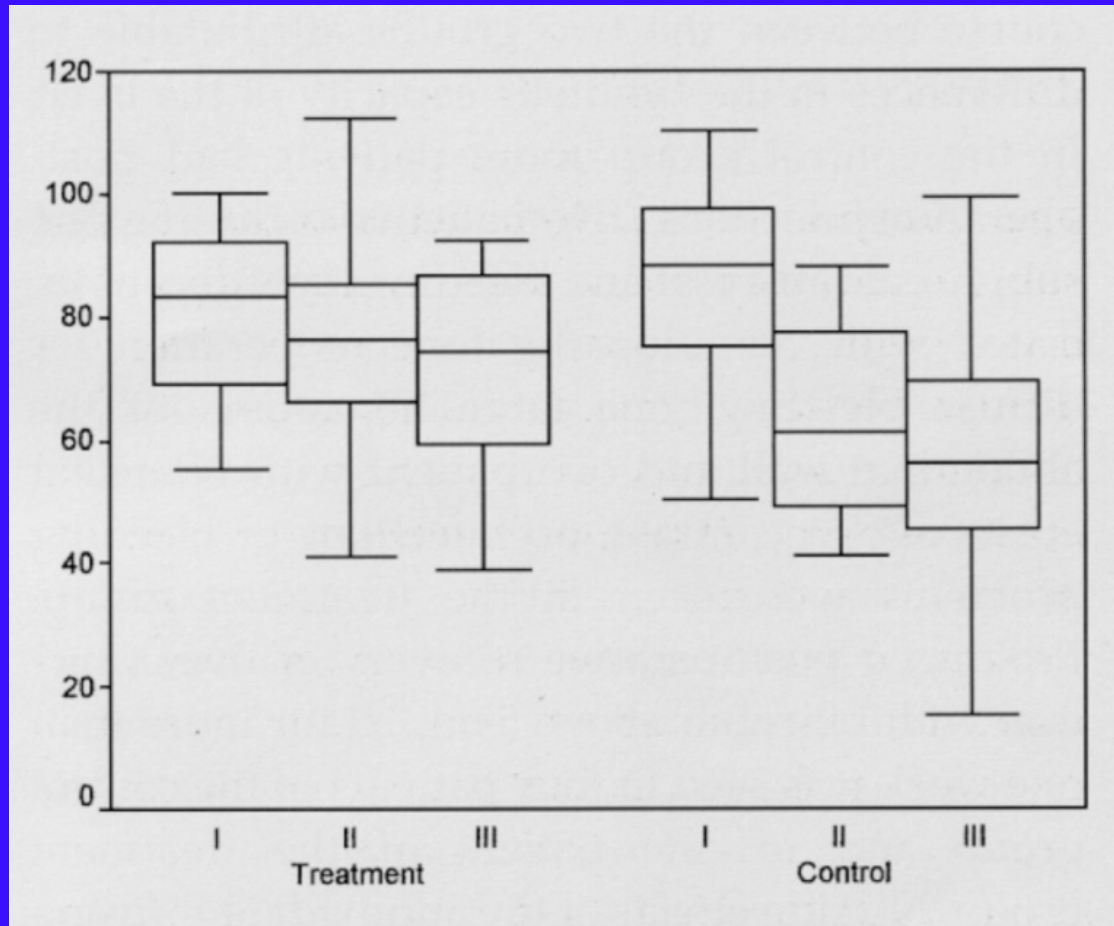


- 1 Sham
- 2 Ischämie
- 3 NaCl
- 4 Cocktail*
- 5 Solvent
- 6 Vit. B Kompl.



Rabl H. et al.: Limitation of intestinal reperfusion injury in the rat by vitamin Treatment. *Med Sci Res* 25, 315-318; 1997

PTT %



geringere Inzidenz

Leberversagen, Blutungskomplikationen u. Infektionen

Cerwenka H, **Rabl H.** Normothermic liver ischemia and antioxidant treatment during hepatic resections. **Free Radical Research** 1999; 30: 463 - 469

Vit E properties

- reduction of ROS
- reduction of lipid peroxides
- prevention of neutrophil accumulation
- reduction of E-selectin expression
- reduction of ICAM-1 expression
- inhibition of NF - kappa B
- inhibition of cyclooxygenase
- inhibition of lipoxygenase

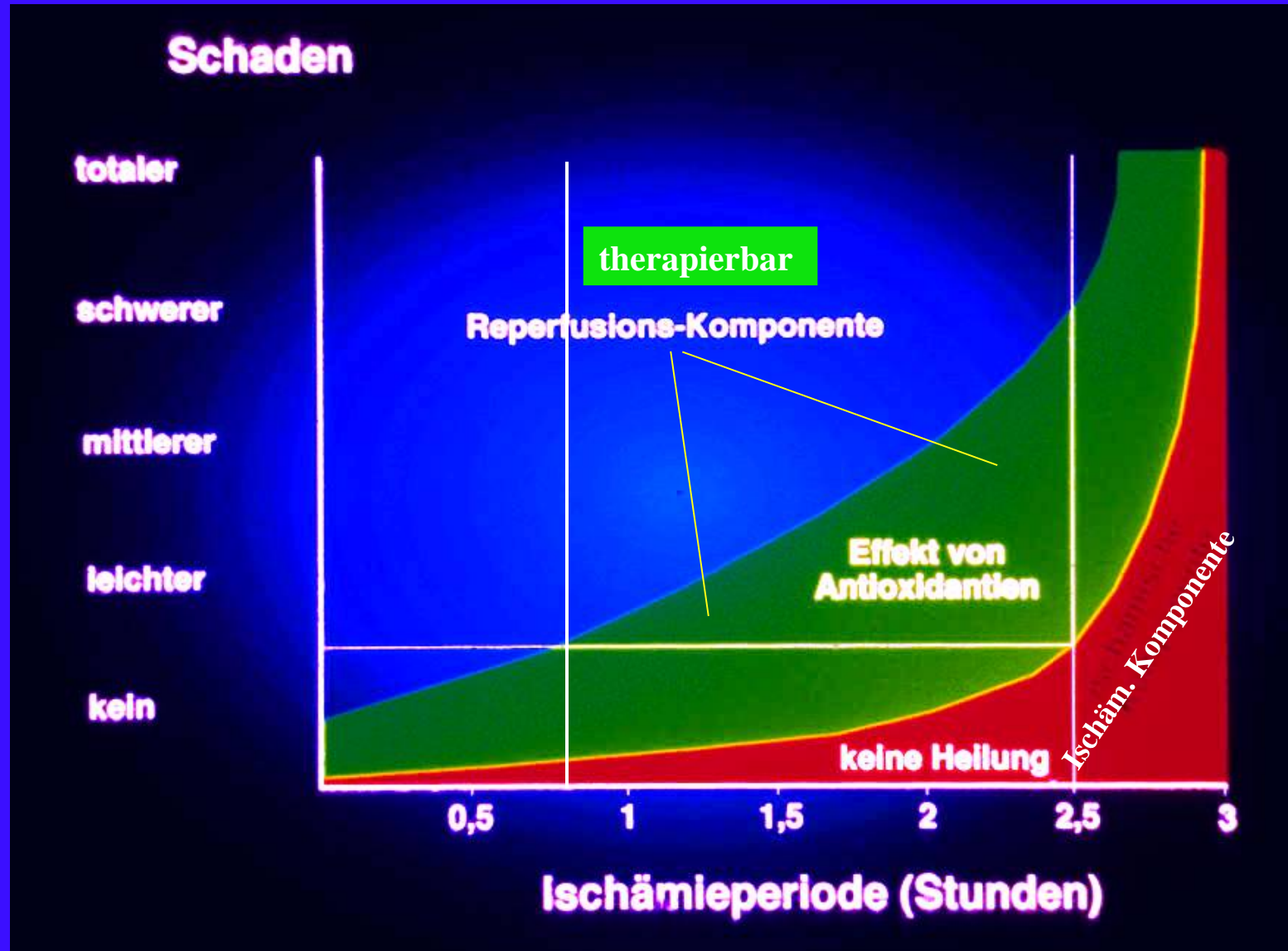
Massey KD. Et al. Am J Physiol 1989; 256:H1191-1199

Formigli L. et al. Histol Histopathol 1997; 12 (3): 663-669

Lehr HA et al. Microcirculation 1998; 5: 117-128

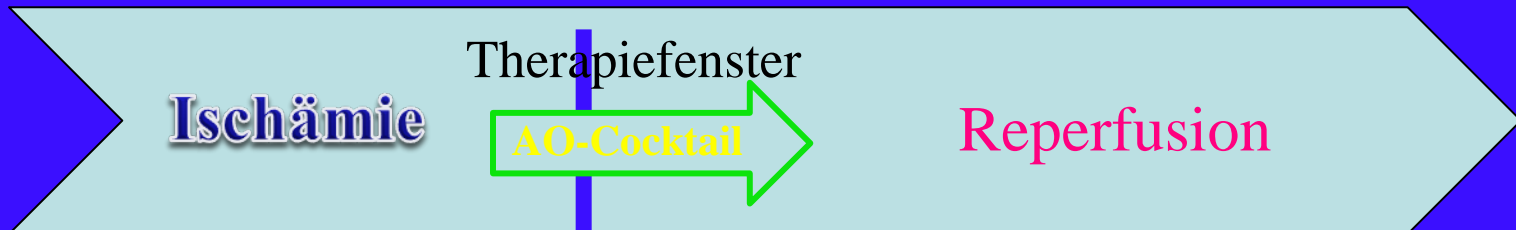
Bonventre JV. Kidney Int 1993: 43:1160-78

Ischämie- / Reperfusionsschaden



Therapiefenster

Radikalfänger (zB. Vitamine) müssen
zur richtigen **Zeit** (Therapiefenster)
am richtigen **Ort** in einer
geeigneten **Konzentration**
zur Verfügung stehen



Therapeutic strategies to attenuate I/R injury.

Controlled, Graded Reperfusion

1

Ischemic Preconditioning

1

Aspirin-Triggered Lipoxin (ATL) Analogues

3

Antioxidant Therapy

Superoxide Dismutase (SOD)

Iron Chelators

Mannitol

N-acetylcysteine (NAC)

Vitamin E

Thiols

Allopurinol

Catalase

2

Calcium Antagonists

1

Angiotensin-Converting Enzyme (ACE) Inhibitors

1

Anti-Complement Therapy

Recombinant, Humanized, Single-Chain Anti-C5 Antibody (h5G1.1-scFv)

Soluble Complement Receptor-1 (sCR1)

1

Leukocyte Depletion / Filtration

3

Anti-Cytokine or Leukocyte Adhesion Molecule mAb

3

Antisense-Oligodeoxynucleotides (ODNs) and Transcription Factor Decoys

3

Endothelin Receptor Antagonists

3

Platelet Activation Factor (PAF) Antagonists

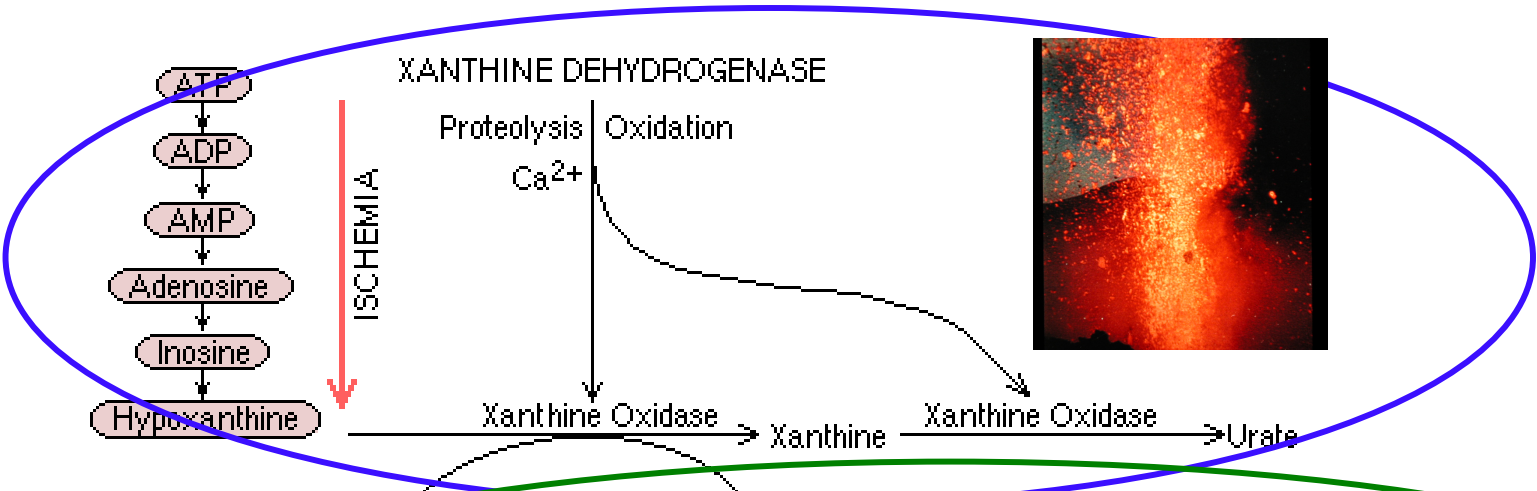
3

Leukotriene-B₄ (LTB₄) Antagonists

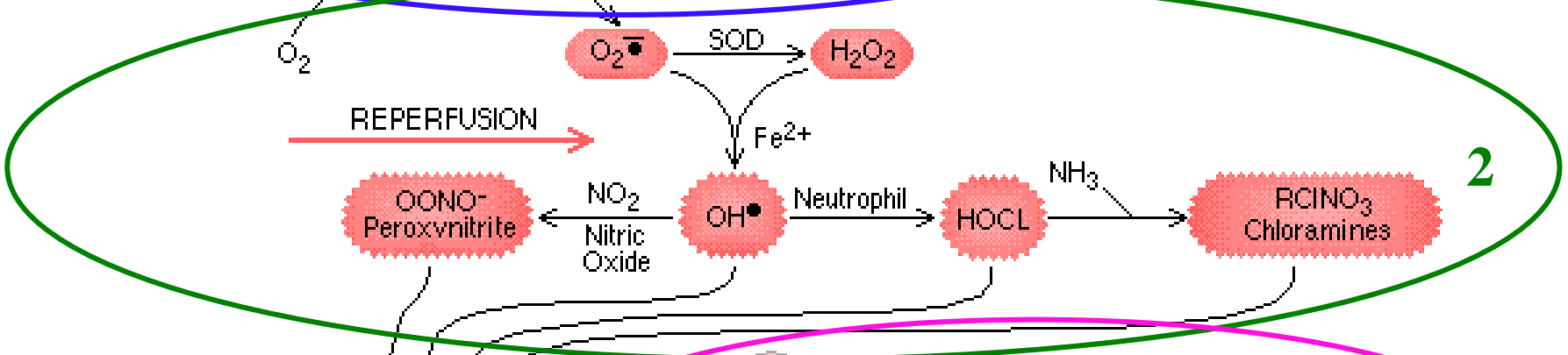
3

Stadien

1



2



3



Erfrüerungen, Unterkühlung, Schock

ATP

AMP

Adenosin

Hypo- / Xanthin



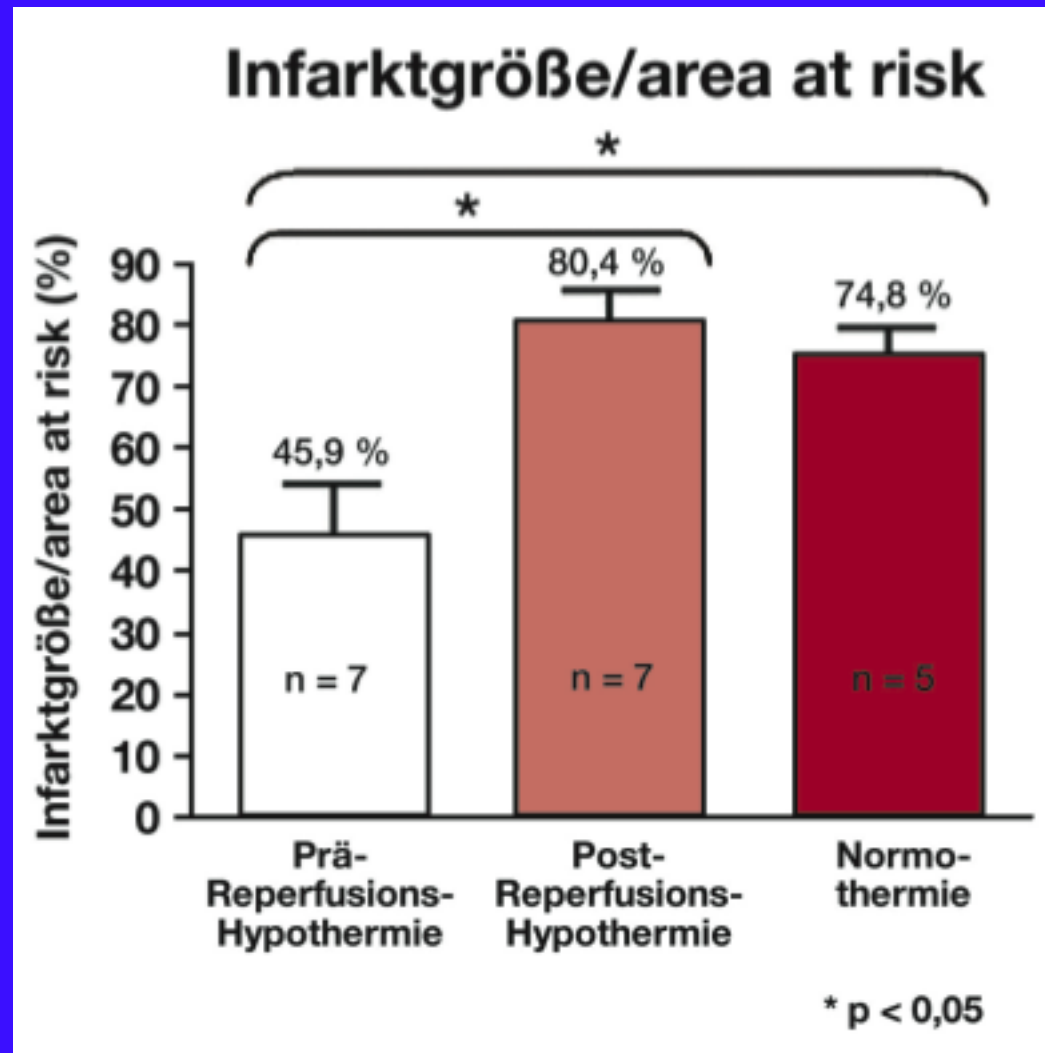
Harnsäure

+

O₂ Radikale

Milde therapeutische Hypothermie (32 – 35°C) beim Myocardinfarkt

Götberg M et al. Rapid short duration hypothermia before reperfusion reduces microvascular obstruction and myocardial infarct size.
BMC Cardiovasc Disord 2008; 8: 7



Milde therapeutische Hypothermie (32 – 35°C) beim Myocardinfarkt

Minnesota: milde HoT führt bei 80% der Überlebenden mit OHCA zu positivem neurolog. outcome – **Nutzen fürs Gehirn !!!**

COOL-MI
ICE-IT
RAPID-MI-ICE
CHILL-MI

STATIM 2013 Vienna
(cooling in myocardial infarction)

Hörmann P et al.
J Kardiol 2012;19 (9-10):274-76

Tabelle 1: Subgruppenanalyse COOL-MI und ICE-IT. Mod. nach [4].

	Infarktgröße (in % des links-ventrikulären Myokards)		p-Wert
	Hypotherme Gruppe	Normotherme Gruppe	
COOL-MI (392 Patienten)			
Gesamtpopulation	13,8	14,1	0,86
Subgruppe mit Vorderwand-STEMI und < 35°C bei Revaskularisation	9,3	18,2	0,05
ICE IT (228 Patienten)			
Gesamtpopulation	10,2	13,2	0,14
Subgruppe mit Vorderwand-STEMI und < 35 °C bei Revaskularisation	12,9	22,7	0,09

Ischemic preconditioning

Murry CE et al. 1986

wiederholte, kurze subletale Ischämieperioden (zB. 5 x 5 min.)
gefolgt von Reperfusionsperioden (zB. 5 x 5 min.) schützen das
zugrundeliegende Gewebe nach verlängerten Ischämieperioden
vor nachfolgendem Zelluntergang

75% Reduktion der Infarktgröße (Tiermodell)

Murry CE et al. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; 74: 1124

Mechanisms of Preconditioning

brief ischemia

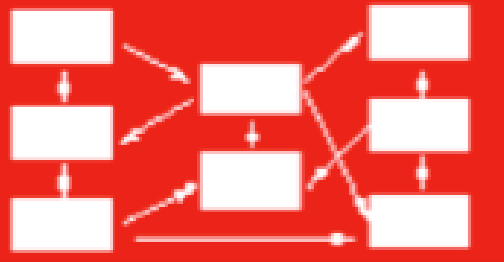


receptor stimulation

G-protein coupled receptors, including adenosine A1/A3, etc



signal transduction



Components may include PKC; InsP3
MAP kinases; ???



phosphorylation of end-effector

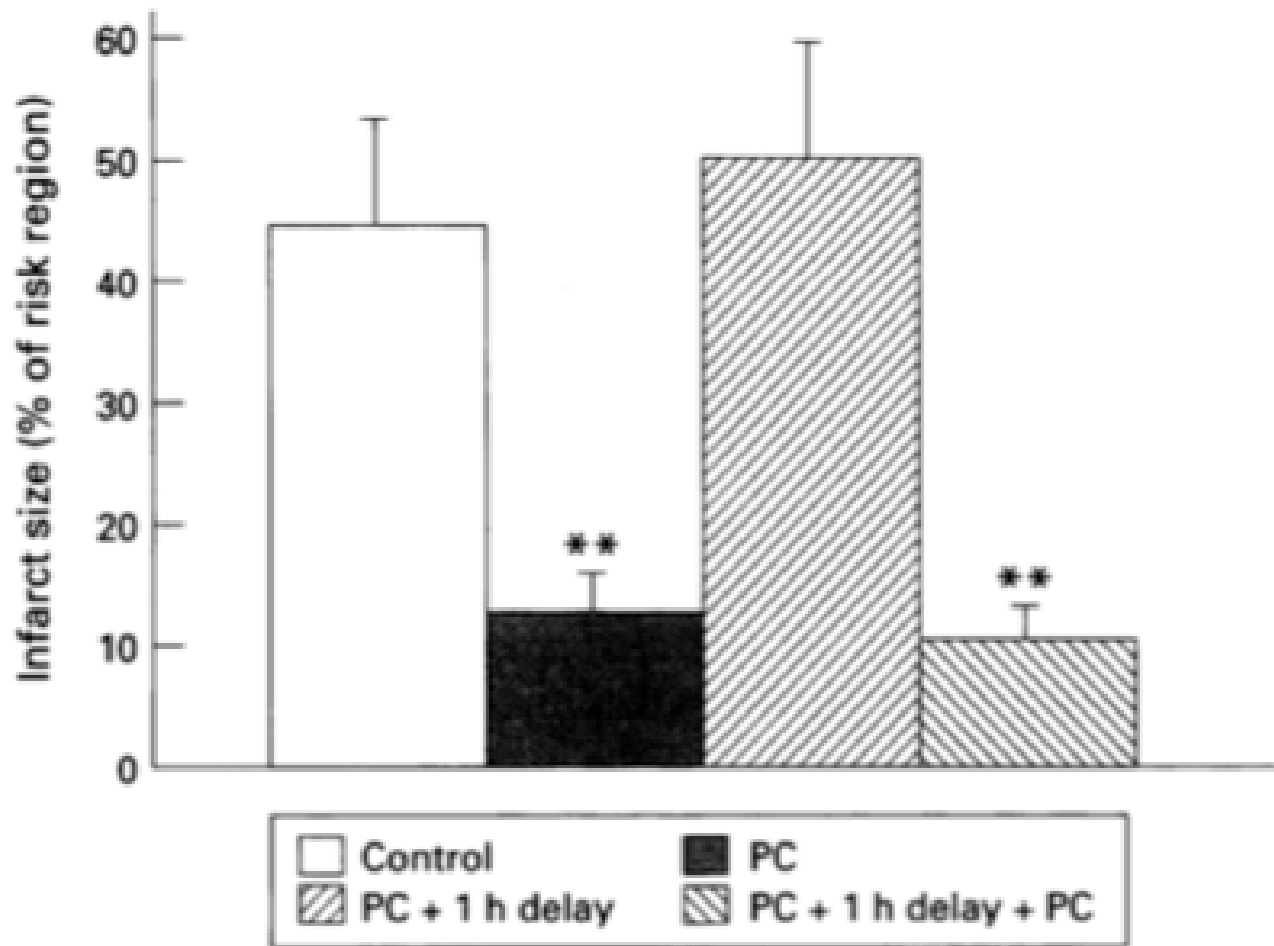
ATP-sensitive potassium channels; ???



CARDIOPROTECTION

Pryzyklenk K. Ischemic preconditioning: exploring the paradox.
Prog Cardiovasc Dis 1998;40:517-47

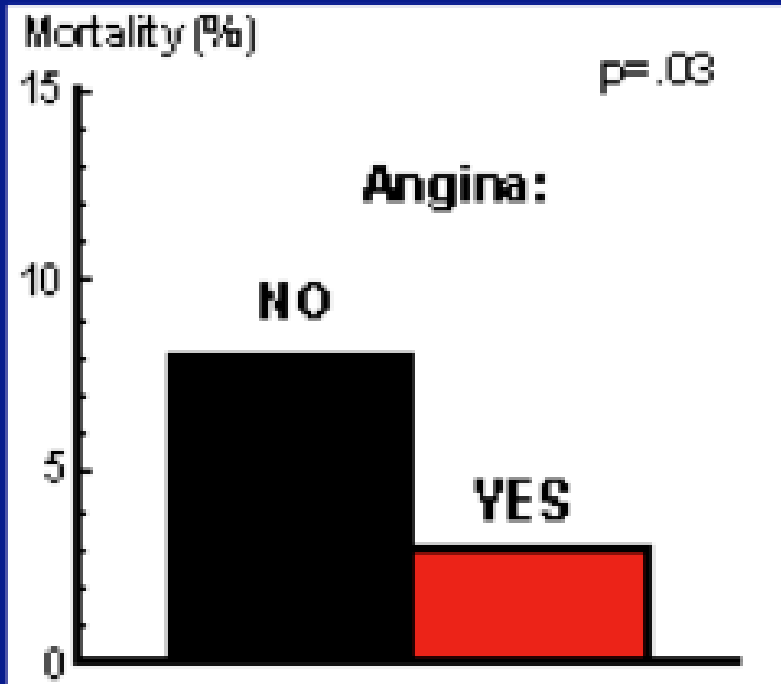
Cardioprotection by recapturing of ischemic preconditioning



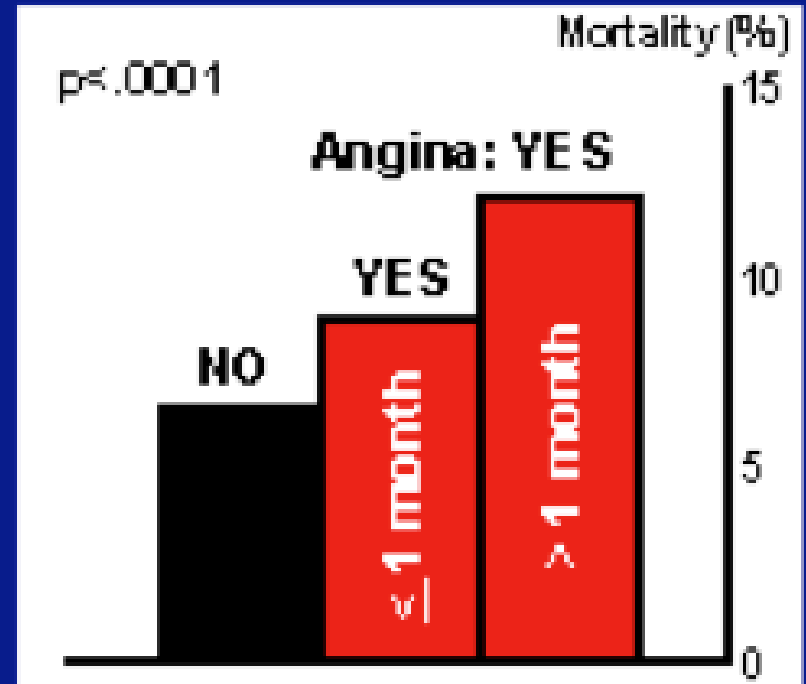
Li Y. Cardioprotective effects of ischemic
Preconditioning can be recaptured after they are lost.
Am J Coll Cardiol 1994; 23:470-4

Effect of Preinfarct Angina on In-Hospital Mortality

A.



B.

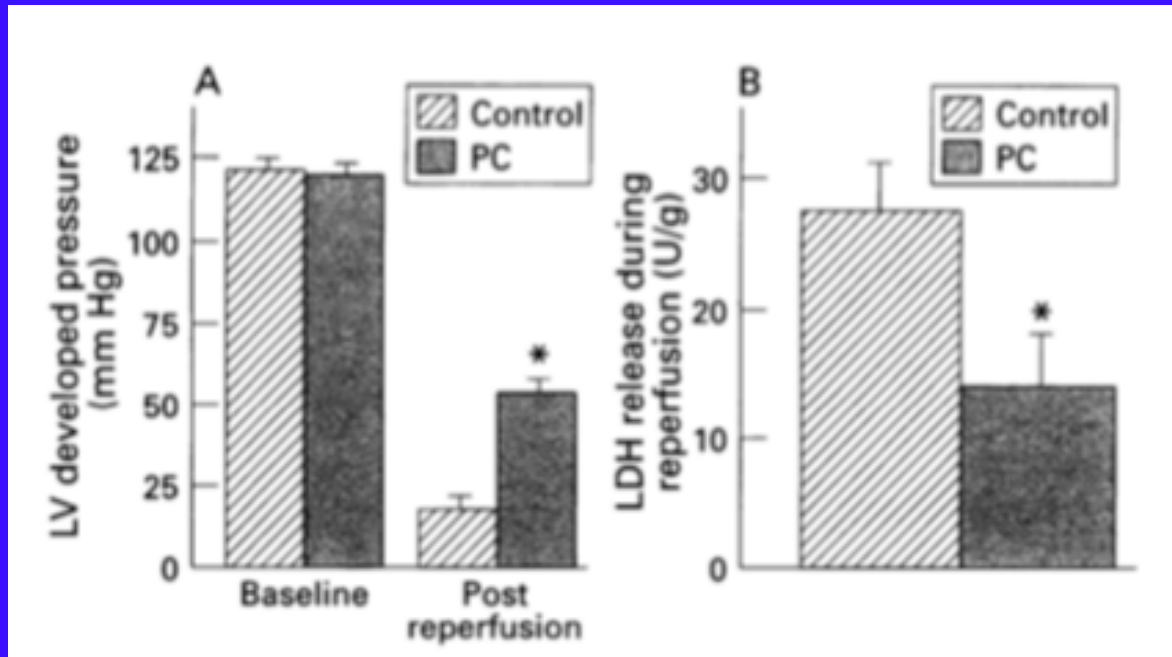


Kloner RA. TIMI-9B. Circulation 1995;91:37-47

Barbash GI. Intern. Tissue Plasminogen Activator / Streptokinase Mortality Trial.

J Am Coll Cardiol 1992;20:36-41

IP and LV-pressure, LDH-release



Weselcouch EO. Inhibition of nitric oxide synthesis does not affect ischemic preconditioning in rat hearts. *Am J Physiol* 1995;268:H242-9

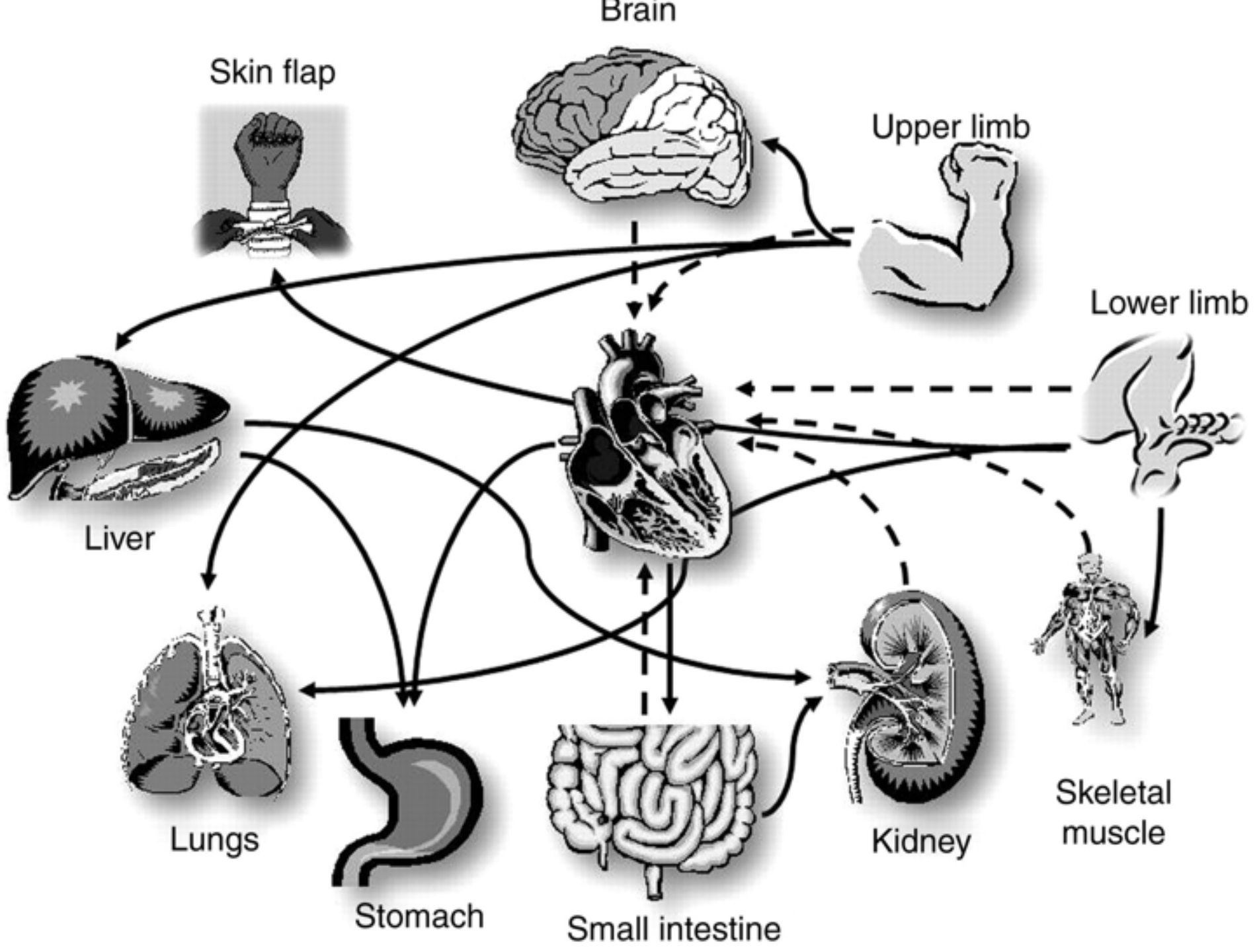
Remote Ischemic Preconditioning

Erhöhte Ischämieresistenz

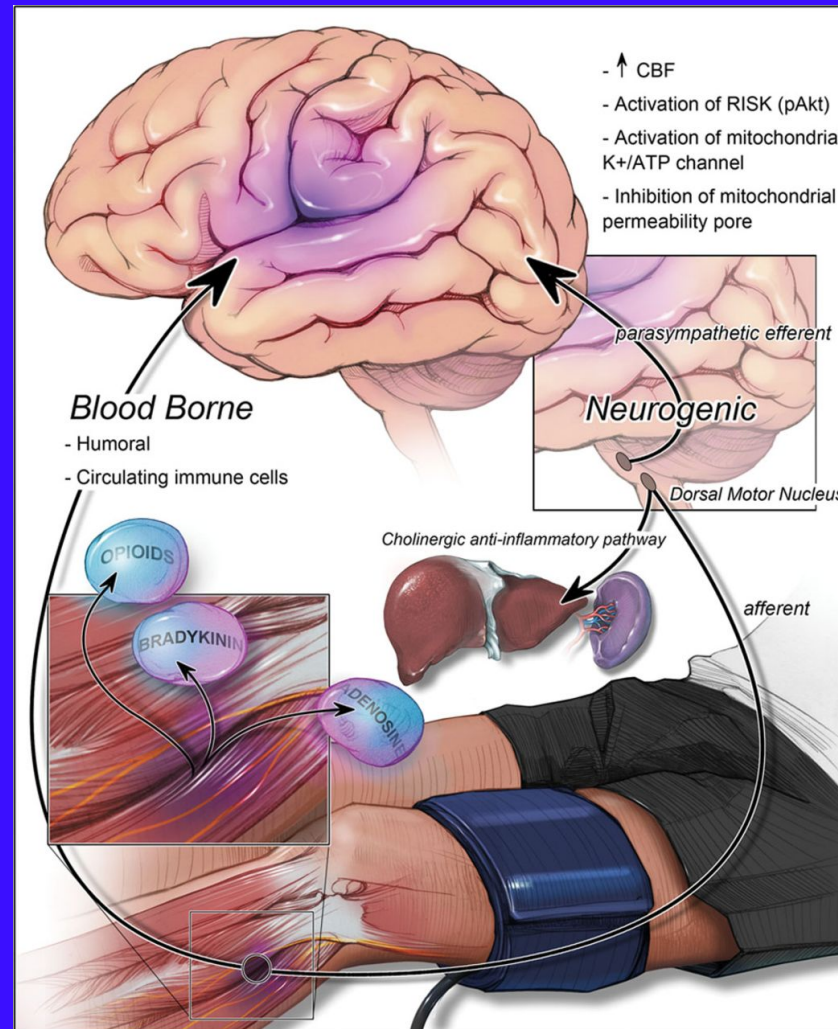
eines beliebigen Organs

nach einer absichtlich in einem Skelttmuskel

ausgelösten Ischämie



Proposed mechanisms of how blood pressure cuff inflation on the leg may lead to neuroprotection during ischemic stroke.



Hess D et al. Stroke 2013;44:1191-1197

RIP reduced myocardial injury in CABG patients

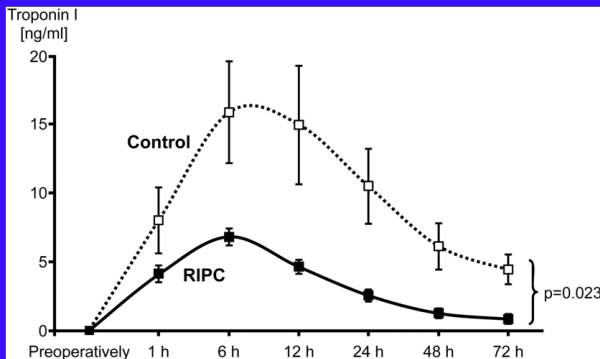
3 x 5 min ischemia by upper left arm cuff (200 mm Hg)
followed by 5 min reperfusion for 3 times

mortality 1,9 vs. 6,9%

Major adverse effect:

cardial and cerebrovascular 13,9 vs. 18,9%

86% less likely to die from heart attack
or stroke, 1 year after surgery



Brain Publikationen

1. Upper limb ischemic preconditioning prevent recurrent stroke in intracranial arterial stenosis. *Neurology* 2012;79:1853-61
2. Remote ischemic preconditioning : making the brain more tolerant, safely and inexpensively. *Circulation* 2011;123:709-711
3. Preconditioning the brain: moving on to the next frontier of Neurotherapeutics. *Stroke* 2012;43:1455-57
4. Limb remote ischemic postconditioning protects against focal ischemia in rats. *Brain Res* 2009;1288:88-94
5. Limb ischemic preconditioning attenuates cerebral ischemic injury in rat model. *Perfusion* 2013; 3:

CONCLUSIO

- Gesamtschaden (Ischämie- und Reperfusionskomponente)
- Therapeutisches Zeit-FENSTER – Schlüssel für Therapieerfolg!!!!

- Antioxidantien

- Milde Hypothermie

(32 – 35°C)

Reperfusionsschaden

- Induzierte Ischämie

- local ischemic preconditioning

- remote ischemic preconditioning

wirksam gegen