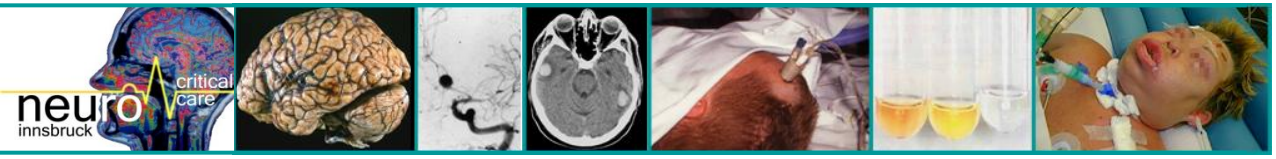

DIAGNOSTIC AND THERAPEUTIC MANAGEMENT OF CEREBRAL VASOSPASM AFTER SAH

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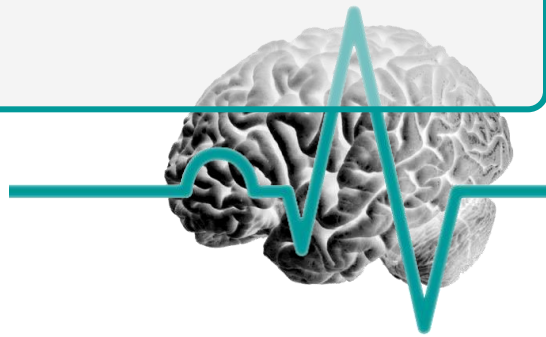
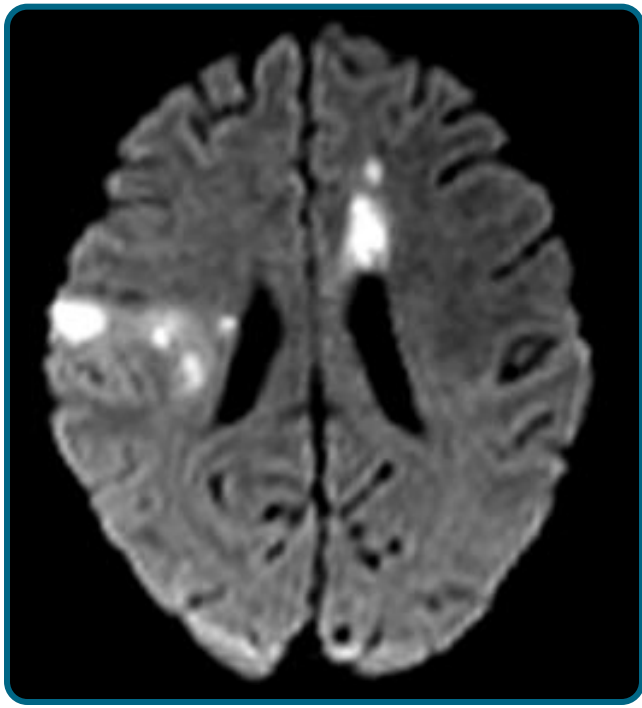


Complications of SAH – Vasospasm and DCI

- **Definition** and **Epidemiology**
  - **Transitory arterial vasoconstriction**, which is seen **72 hours or later after the hemorrhage with a maximum around day 7**
    it lasts usually no **more than 15** (rarely 20) **days**
  - **50–75%** of angiographies: narrowing of th lumen

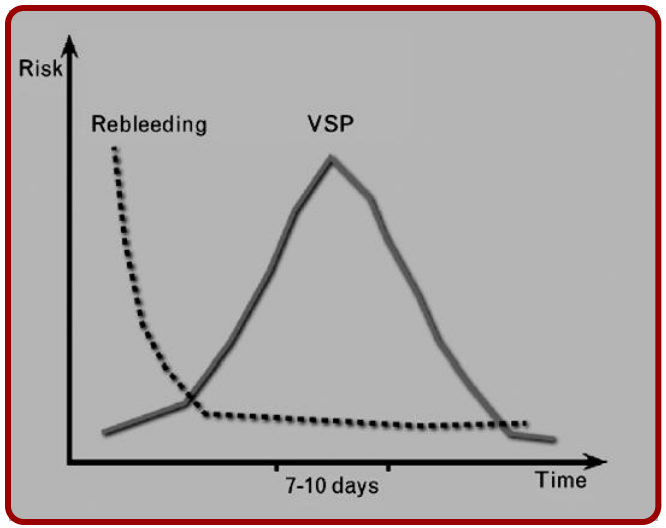


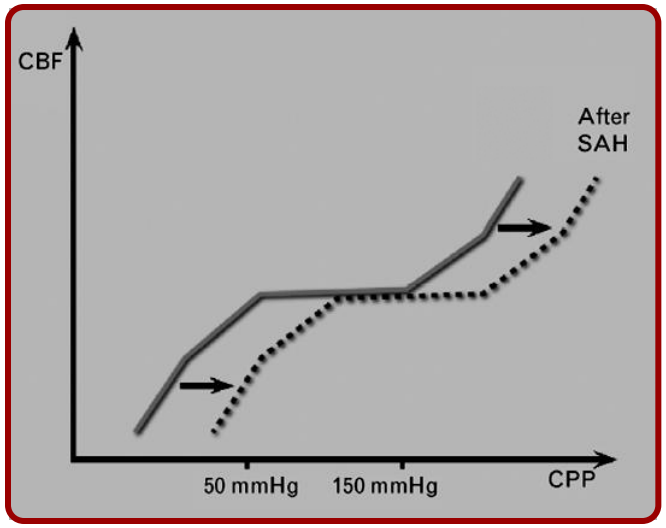
- ***"Delayed cerebral ischemia"*** (**DCI**)
  "Delayed ischemic neurological deficit" (**DIND**)
  - This vasoconstriction manifests clinically only **in ca. 30–50%**
  - Not all patients develop a vasospasm (**complex pathophysiology**)
  - DCI causes in **25% permanent neurological sequelae or, even, death**

Pathophysiology

- Delayed and reversible **vasculopathy**
- **Disturbance of regualatoy mechanisms of the vasculature-tone**
  (Imbalance of endogenous vasodilatators and endogenous vasoconstrictors)
- **Liberation of "spasmogenic" substances** when subarachnoidal blood is lysing
- **Impaired capacity of autoregulation** (CBF-reduction)
- **Hypovolemia** (reduction of regional CPP)
- (Local) **activation of** coagulation cascade leading to formation of **microthrombi**

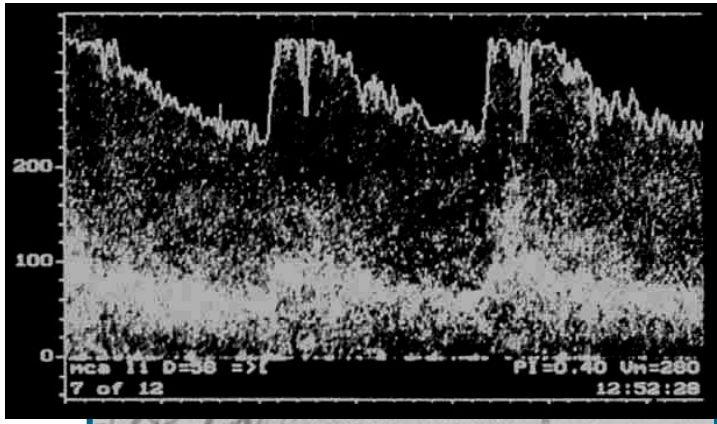
Lackner et al , 2010



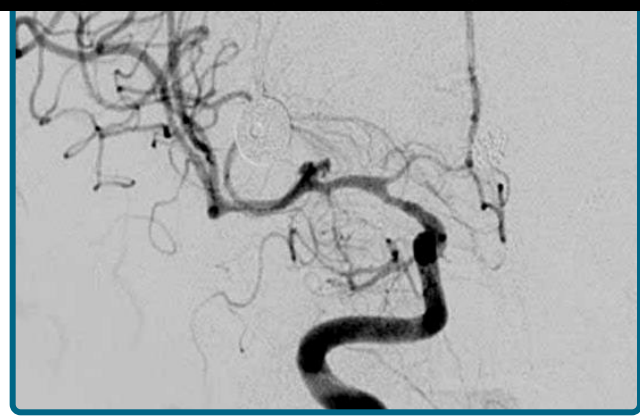


Complications of SAH – Vasospasm and DCI

- **Diagnostic procedures**
  - in awake patients: clinical - neurological exam
  - **Technical diagnostic means in patients with impaired consciousness or when analgosedated**

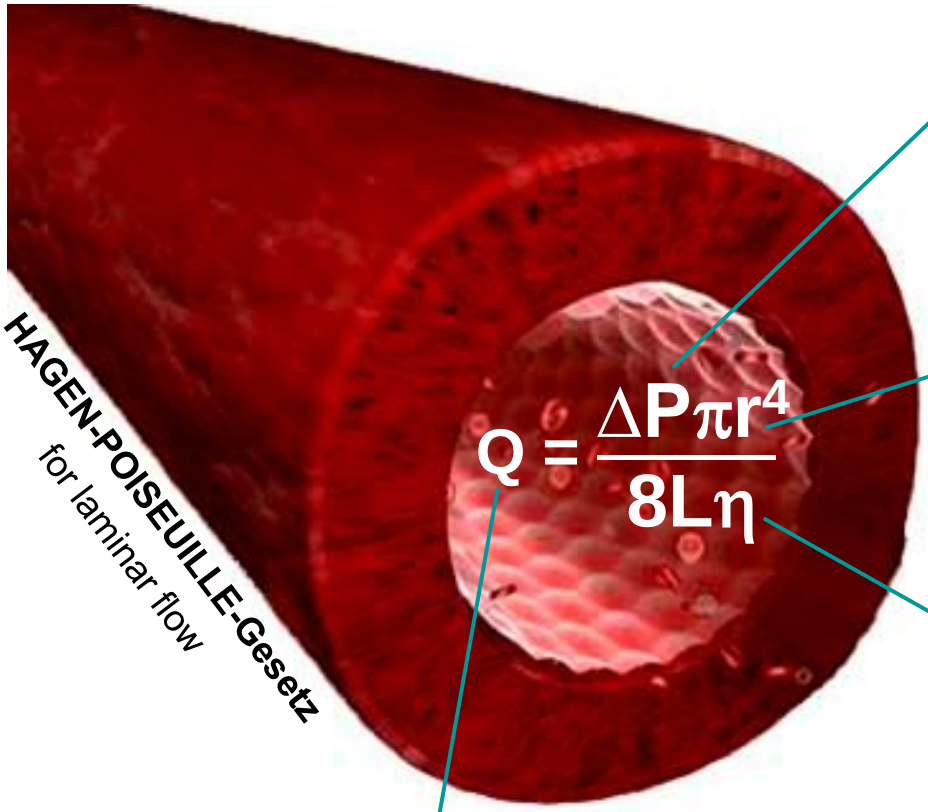


- **cerebral panangio**



- **CT- , MR-Angiography**
  (incl. Perfusion-CT/MR)
- **Neurosonography** (TCD)
  - **increased mean bloodflow velocity** (**v_{mean} > 120 cm/s**)
  - **increase of v_{mean} ≥ 50%**
  - **MCA/ICA** (LINDEGAARD)-Index **> 3**
- **further monitoring methods** cerebral microdialysis, **ptiO2**, PET

possibilities of intervention



Perfusion pressure

controlled (permissive) hypertension

Radius/Diameter

prophylaxis/ therapy of „vasoconstriction“

Viscosity

Hemodilution

cerebral bloodflow

„neuroprotection"

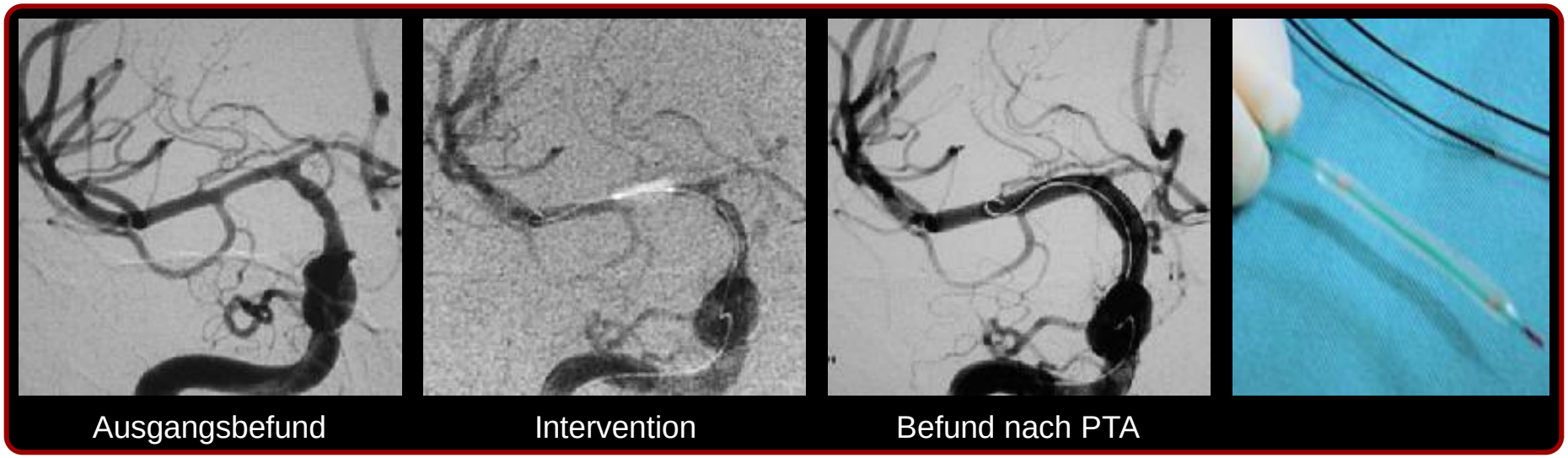
	Efficacy
– ▷**Prophylaxis of Vasospasm**	
– **Reduction/ Cleaning** of subarachnoid blood/hematoma	
mechanically (e.g. rinsing during surgery)	**?**
pharmacologically	**?**
fenestration of the lamina terminalis, lumbar drainage	**?**
– **Modulation** of **inflammatory mechanisms**	Theory
– **Inactivation / blockade** of spasmogenic substances	
free radical scavengers, anti-oxydants	**(+)/ –**
iron chelating agents	**?**
Endothelin-receptor antagonists	**+++**
– **Blockade** of **constriction** of muscles of the blood vessels	
(Systemic) Calcium-channel blocking agents	**(+)**
(Local) *"prolonged-release"* polymers	**++**

Cerebral Vasospasm – Therapeutic possibilities

Efficacy

+++

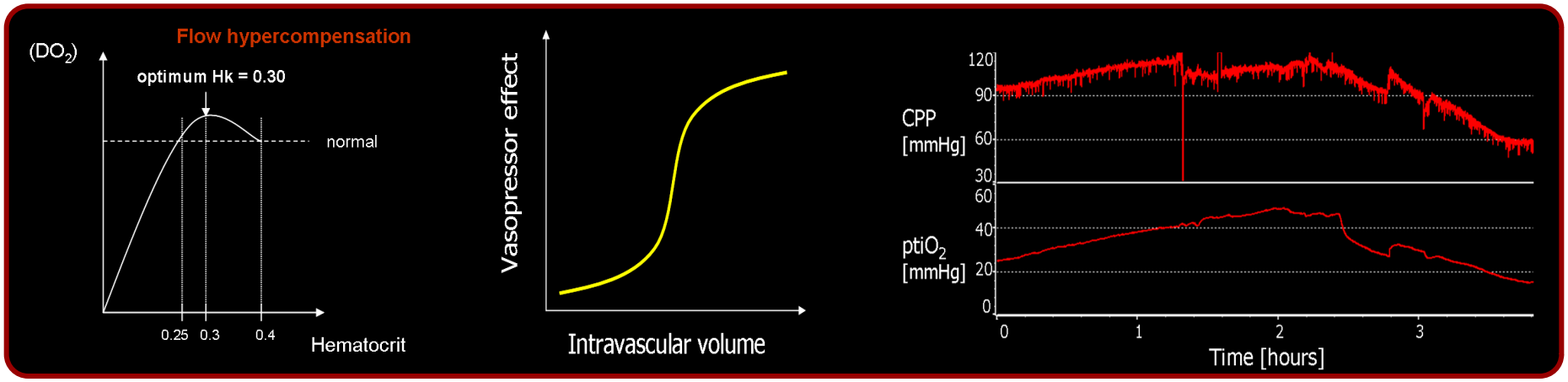
- Transluminal **Balloon-Angioplasty**
  - **Technical limitations**, only possible in large-diameter vessel portions (ICA, M1, BA, VA, A1)



  - In **ca. 90%** prolonged effect
  - **rapid re-constriction** seen in **ca. 10%**
  - **thromboembolic events** (ca. 5%) und **rupture of the vessel** (!!) as substantial complications – **therefore abandoned**

Cerebral Vasospasm – Therapeutic possibilities

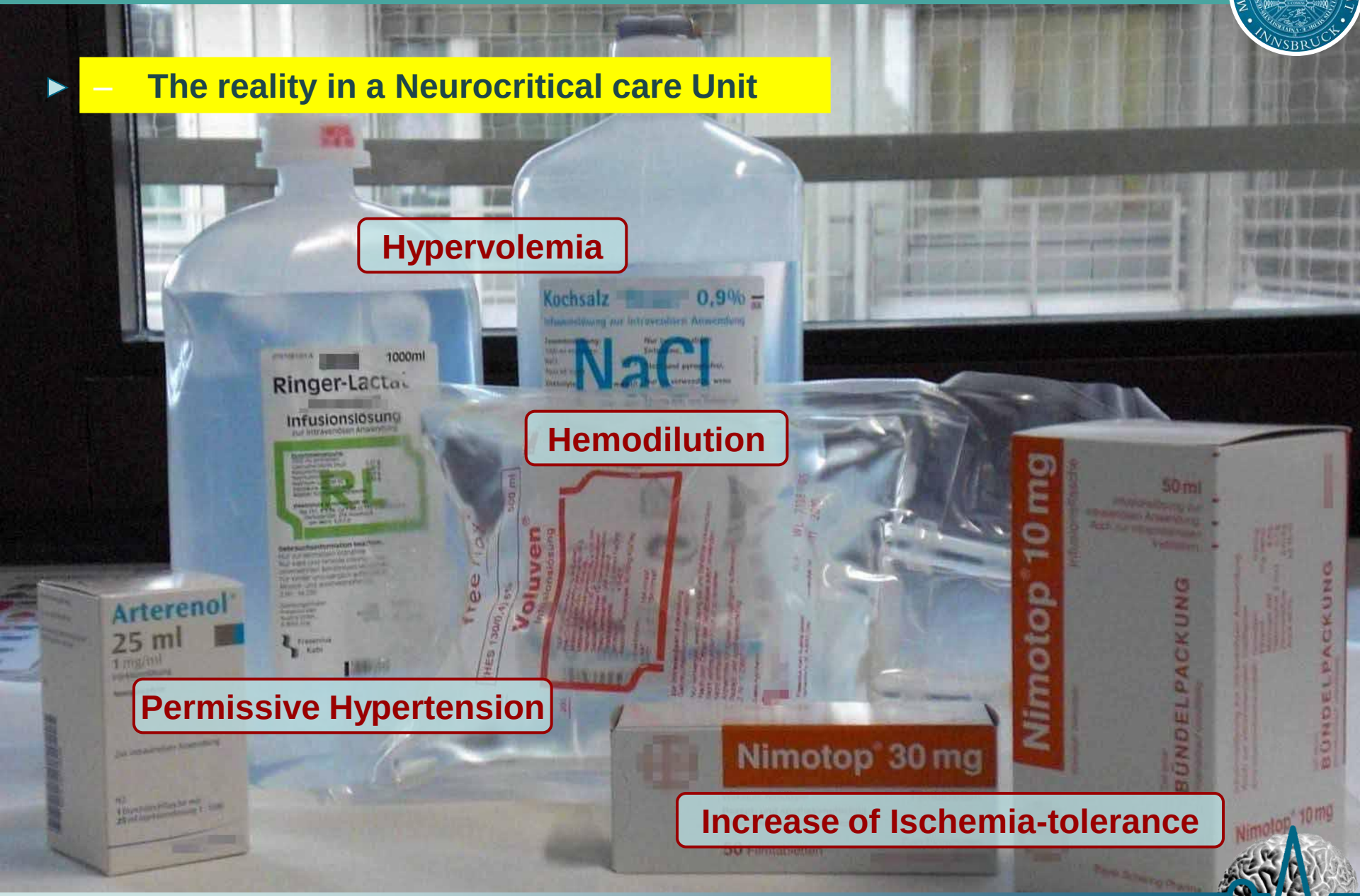
	Efficacy
Intra-arterial pharmacologic **Vasodilatation (as bolus)**	**+++**
– temporary effect	
– various agents with different mode of actions, e.g. Papaverin, **Nimodopin (i.a.pressure pump delivery over 24 h – persisting effect),** Verapamil, Milrinon, Fasudil	
– Optimisation of cerebral hemodynamics (**HHH-therapy**)	**(+)**



– Therapeutic **Hypothermia – targeted temp. management**	**?**

Cerebral Vasospasm – Therapeutic possibilities

- **– The reality in a Neurocritical care Unit**



Cerebral Vasospasm – Therapeutic possibilities

- **General therapeutic management**
  - Admission to (**N)ICU with advanced systemic and cerebral (neuro-) monitoring**
  - Maintenance and reestablishment of appropriate **oxygenation, perfusion** and **metabolic Homoiostasis**
  - **Prevention of hypovolemia**, **fever**, **hypo- and hyperglycemia** and **electrolyte derangements**
  - **Prophylaxis** and **therapy of infections**

- **Prophylactic administration of** the calcium channel blocker **Nimodipin** (Nimotop®)
  - Recent studies prove the equal efficacy of **oral** (5–6mal 60 mg/d) and **intravenous application** (continuous1–2 mg/h) **.**
    HOWEVER: CAVE malabsorption
  - *Cave:* **hypotensive effect of nimodipine ➔** sufficient MAP/CPP is essential

- continuous administration of **Magnesium➔normal Mg-level!**
  Cave: **Hypotension !!**

Cerebral Vasospasm – Therapeutic possibilities

- **HHH-Therapy** (therapeutic **Hypertension**, **Hypervolemia** und **Hemodilution**) ➔ **H(HH)**
  - in patients with **neurologic (focal) signs and symptoms** or newly developed **cerebral infarction** (cCT) =(DCI) due to vasospasm
  - **generous administration of volume** together with **vasopressors** (e.g. noradrenalin, phenylephrin) and **inotropic agents** (e.g.dobutamine)
  - **Hemodilution** (questionable efficacy) – colloidal infusions (e.g.HES)
  - **rate of complications: ca. 20–30%** volume overload, **pulmonary edema**, **cardiac insufficiency**, **derangement of coagulation and electrolytes**
  - advanced **cardiac**, **hemodynamic** and **pulmonary MONITORING** essential and obligatory, in particular in **patients at risk**

Endothelin-Receptor-Antagonists

Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage (CONSCIOUS-1)

Randomized, Double-Blind, Placebo-Controlled Phase 2 Dose-Finding Trial

Table 2. Extended Glasgow Outcome Scale for the All-Treated Set*

		Clazosentan		
Characteristic	Placebo (n=96)	1 mg/hour (n=107)	5 mg/hour (n=110)	15 mg/hour (n=96)
Death, vegetative, or severe disability	30 (31)	28 (26)	30 (27)	33 (34)
Exact 95% CI	22–42%	18–36%	19–37%	25–45%
Absolute risk reduction		−5%	−4%	3%
Exact 95% CI		−18–8%	−17–9%	−11–17%
P value (Fisher exact test)		0.44	0.54	0.76
Relative risk reduction		0.16	0.13	−0.10
95% CI (normal approximation)		−0.29–0.46	−0.34–0.43	−0.65–0.27

– **CONSCIOUS-2** (C2)(Clipping) and **CONSCIOUS-3** (C3)(Coiling)

mid 2010: C2 completed, End 2010: C3 prematurely terminated

Moddified acc to Macdonald RL et al., Stroke 2008;39:3015–3021

Erythropoietin

Acute systemic erythropoietin therapy to reduce delayed ischemic deficits following aneurysmal subarachnoid hemorrhage: a Phase II randomized, double-blind, placebo-controlled trial

TABLE 2: Results of primary end points

Primary End Points	Total (%)	Placebo (%)	EPO (%)	p Value
vasospasm*				
yes	27 (33.8)	16 (40.0)	11 (27.5)	0.24
no	53 (66.2)	24 (60.0)	29 (72.5)	
ipsilat side				
yes	24 (30.0)	14 (35.0)	10 (25.0)	0.33
no	56 (70.0)	26 (65.0)	30 (75.0)	
contralat side				
yes	17 (21.32)	11 (27.5)	6 (15.0)	0.17
no	63 (78.8)	29 (72.5)	34 (85.0)	

TABLE 2: Results of primary end points

Primary End Points	Total (%)	Placebo (%)	EPO (%)	p Value
severe vasospasm†				
yes	14 (17.5)	11 (27.5)	3 (7.5)	0.037
no	66 (82.5)	29 (72.5)	37 (92.5)	
ipsilat side				
yes	11 (13.8)	9 (22.5)	2 (5.0)	0.014
no	69 (86.2)	31 (77.5)	38 (95.0)	
contralat side				
yes	6 (7.5)	4 (10.0)	2 (5.0)	0.43
no	74 (92.5)	36 (90.0)	38 (95.0)	

Days of Impaired Autoregulation‡	Total	Placebo	EPO	Difference	p Value
ipsilat side	5.0 ± 4.1 (4.1–5.9)	6.6 ± 4.3 (5.2–8.0)	3.5 ± 3.1 (2.5–4.4)	3.2 (1.5–4.9)	<0.001
contralat side	3.7 ± 3.6 (2.9–4.5)	4.3 ± 3.9 (3.1–5.6)	3.0 ± 3.1 (2.0–4.0)	1.3 (–0.2–2.9)	0.10

– **Erythropoetin alpha** (e.g. Erypo®) i.v. 30 000 U in 30 min for 3 consecutive days (total dosage 90 000 U)

Modifiziert nach Tseng MY et al., J Neurosurg 2009;111:171–180

Statins

A Randomized, Double-Blind, Placebo-Controlled Pilot Study of Simvastatin in Aneurysmal Subarachnoid Hemorrhage

Table 3. Exploratory Analyses of VSP Indices and Clinical Outcome

	Placebo (n=20)	Simvastatin (n=19)	*P*
Conventional angiography for VSP	10 (50%)	7 (37%)	0.41
Conventional angiographic VSP	8 (40%)	5 (26%)	0.50
CT angiography for VSP	11 (55%)	12 (63%)	0.89
CT angiographic VSP	8 (40%)	10 (53%)	0.43
TCD PSV_{MCA}>200 cm/sec and Lindegaard ratio >3*	10 (50%)	13 (68%)	0.24
No. of days PSV_{MCA}>200 cm/sec (median, 25% to 75%)	1 [0–5]	4 [1.25–7.5]	0.11
Time to PSV_{MCA}>200 cm/sec (days, ±SD)	4.8±1.4	5.9±2.0	0.15
Maximum PSV_{MCA}, cm/sec±SD	227±84	253±49	0.3
No. of days of HH (median, 25% to 75%)	2 [0–7]	2 [0–7.75]	0.86
Endovascular intervention for VSP	6 (30%)	5 (26%)	0.71
Total intra-arterial nicardipine, mg±SD	7±13	11±21	0.48

Table 3. Exploratory Analyses of VSP Indices and Clinical Outcome

	Placebo (n=20)	Simvastatin (n=19)	*P*
DIND	10 (50%)	7 (37%)	0.41
Time to DIND, days, ±SD	5.4±1.9	6.2±2.6	0.41
VSP-related infarct on CT or MRI	5 (25%)	2 (11%)	0.41
No. of NICU days, ±SD	12±4	14±5	0.36
No. of hospital days, ±SD	18±9	20±12	0.74
Discharge home	7 (35%)	8 (42%)	0.65
Discharge modified Rankin Scale ≤2	10 (50%)	7 (37%)	0.41

– **Simvastatin** p.o. 40 mg/d or **Pravastatin** p.o. 40 mg/d

Modified acc. Chou SH et al., Stroke 2008;39:2891–2893

Nicardipin *"prolonged-release"* Implantate

Effect of Nicardipine Prolonged-Release Implants on Cerebral Vasospasm and Clinical Outcome After Severe Aneurysmal Subarachnoid Hemorrhage

A Prospective, Randomized, Double-Blind Phase IIa Study

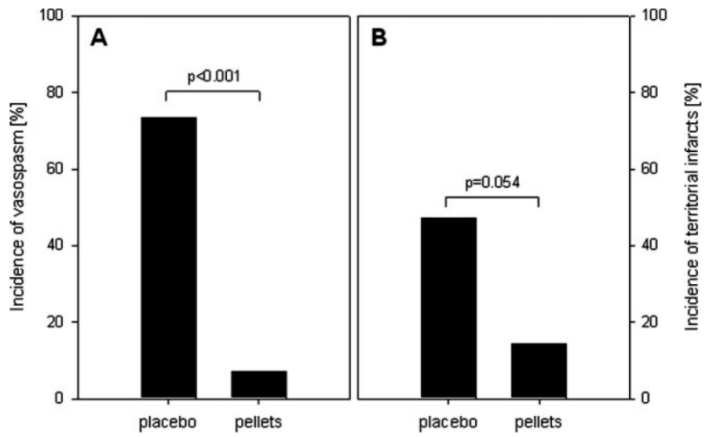
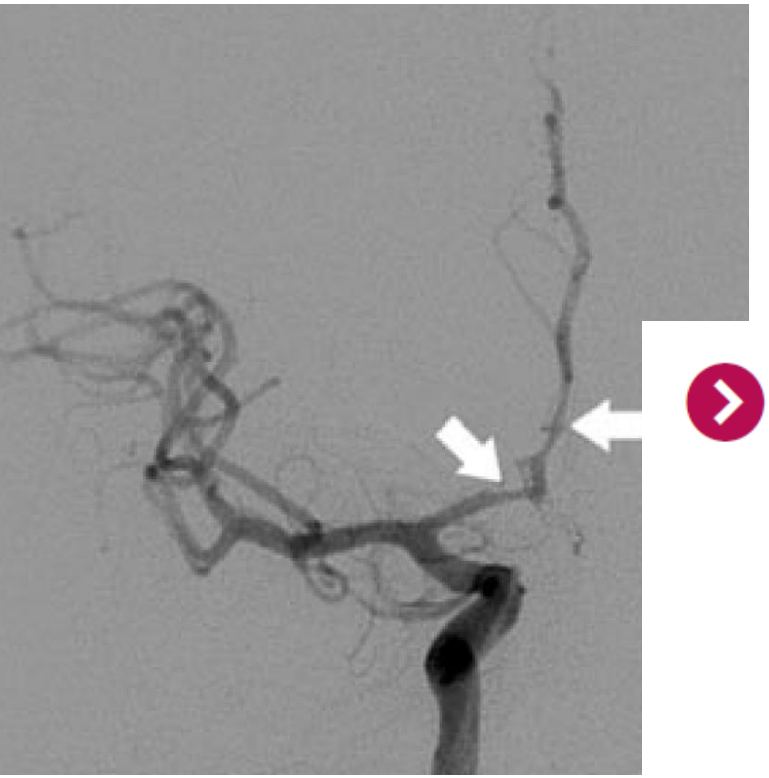


TABLE 3. One-Year Clinical Outcome

	Treatment Groups		*P* Value
	Control (%)	NPRIs (%)	*U* test
Modified rankin scale			
0–2 "good"	38.5 (n=5)	85 (n=11)	
3–4 "moderate"	7.7 (n=1)	7.5 (n=1)	
5–6 "poor"	53.8 (n=7)	7.5 (n=1)	0.0001
National Institutes of Health Stroke Scale			
0–4 "good"	71 (n=7)	100 (n=11)	0.0001

– **NPRIs** (10 Implants à 4 mg Nicardipin)

Modified acc. To Barth M et al., Stroke 2007;38:330–336



From: Schmutzhard, Beer, Vajkoczy, 2010)

- **Die Aufrechterhaltung eines ausreichenden arteriellen Mitteldrucks ist der Nimodipingabe vorzuziehen**

MAP !!!

- **Bei wachen Patienten wird die Diagnose eines DIND klinisch gestellt.**

Awake patient: clinical-neurological exam!!!

Complications of SAH – Vasospasm and DCI

(DCI) **DIND: is it only narrowing of the Lumen- (= „Vasospasm“)?**

Journal of Neurosurgical Anesthesiology
Vol. 12, No. 4, pp. 297–306

Ventricular Cerebrospinal Fluid and Serum Concentrations of sTNFR-I, IL-1ra, and IL-6 After Aneurysmal Subarachnoid Hemorrhage

*Andreas Gruber, *Karl Rössler, **Wolfgang Graninger, †Andrew Donner, †Udo M. Illievich, and *Thomas Czech

*Department of *Neurosurgery; Department of **Internal Medicine I, Division of Infectious Diseases and Chemotherapy Research Laboratories; and †Department of Anesthesiology and General Intensive Care, University of Vienna, Vienna, Austria*

Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION

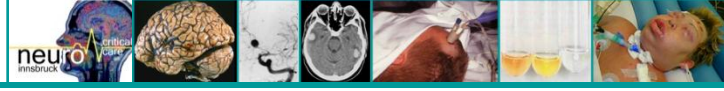
American Stroke Association℠

A Division of American Heart Association

Cellular Microparticles as a Marker for Cerebral Vasospasm in Spontaneous Subarachnoid Hemorrhage

Peter Lackner, Anelia Dietmann, Ronny Beer, Marlene Fischer, Gregor Broessner, Raimund Helbok, Johannes Marxgut, Bettina Pfausler and Erich Schmutzhard

Stroke 2010, 41:2353-2357: originally published online September 2, 2010
doi: 10.1161/STROKEAHA.110.584995
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0039-2499. Online ISSN: 1524-4628



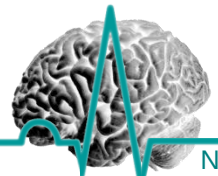
Fischer *et al. BMC Neurology* 2011, **11**:59
http://www.biomedcentral.com/1471-2377/11/59

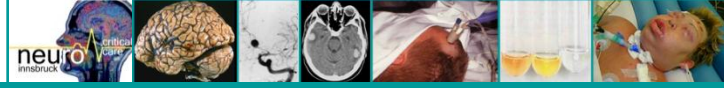
BMC Neurology

RESEARCH ARTICLE Open Access

Angiopoietin-1 is associated with cerebral vasospasm and delayed cerebral ischemia in subarachnoid hemorrhage

Marlene Fischer[1†], Gregor Broessner[1†], Anelia Dietmann[1], Ronny Beer[1], Raimund Helbok[1], Bettina Pfausler[1], Andreas Chemelli[2], Erich Schmutzhard[1] and Peter Lackner[1*]





Original Paper

Cerebrovascular Diseases

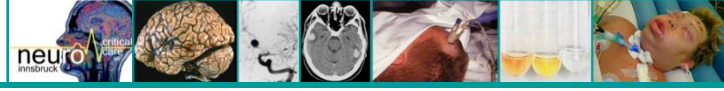
Cerebrovasc Dis 2012;33:16–22
DOI: 10.1159/000331925

Received: November 7, 2010
Accepted: August 2, 2011
Published online: November 30, 2011

Soluble Endoglin and Transforming Growth Factor-β_1 and the Development of Vasospasm after Spontaneous Subarachnoid Hemorrhage: A Pilot Study

Anelia Dietmann Peter Lackner Marlene Fischer Gregor Broessner
Bettina Pfausler Raimund Helbok Erich Schmutzhard Ronny Beer

Department of Neurology, Innsbruck Medical University, Innsbruck, Austria



20 YEARS
Cerebrovascular Diseases

Original Paper

Cerebrovasc Dis 2010;29:576–583
DOI: 10.1159/000306645

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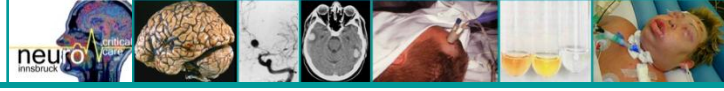
Publish

Association of Platelet and Leukocyte Counts with Delayed Cerebral Ischemia in Aneurysmal Subarachnoid Hemorrhage

K.M. Kasius[a] C.J.M. Frijns[a] A. Algra[a, b] G.J.E. Rinkel[a]

[a]Department of Neurology, Rudolf Magnus Institute of Neuroscience, and [b]Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, The Netherlands

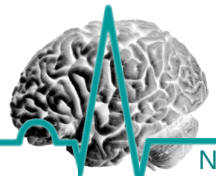


neurocritical care society Neurocrit Care (2011) 15:211–240
DOI 10.1007/s12028-011-9605-9

REVIEW

Critical Care Management of Patients Following Aneurysmal Subarachnoid Hemorrhage: Recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference

Michael N. Diringer · Thomas P. Bleck · J. Claude Hemphill III · David Menon · Lori Shutter · Paul Vespa · Nicolas Bruder · E. Sander Connolly Jr. · Giuseppe Citerio · Daryl Gress · Daniel Hänggi · Brian L. Hoh · Giuseppe Lanzino · Peter Le Roux · Alejandro Rabinstein · Erich Schmutzhard · Nino Stocchetti · Jose I. Suarez · Miriam Treggiari · Ming-Yuan Tseng · Mervyn D. I. Vergouwen · Stefan Wolf · Gregory Zipfel



Research

Open Access

Insulin-related decrease in cerebral glucose despite normoglycemia in aneurysmal subarachnoid hemorrhage

Florian Schlenk[1], Daniela Graetz[1], Alexandra Nagel[1], Maren Schmidt[2] and Asita S Sarrafzadeh[1]

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Received: 21 Aug 2007 Revisions requested: 5 Oct 2007 Revisions received: 1 Dec 2007 Accepted: 24 Jan 2008 Published: 24 Jan 2008

Critical Care 2008, **12**:R9 (doi:10.1186/cc6776)

Effective Glycemic Control With Aggressive Hyperglycemia Management Is Associated With Improved Outcome in Aneurysmal Subarachnoid Hemorrhage

Julius Gene S. Latorre, Sherry Hsiang-Yi Chou, Raul Gomes Nogueira, Aneesh B. Singhal, Bob S. Carter, Christopher S. Ogilvy and Guy A. Rordorf

Stroke 2009;40;1644-1652; originally published online Mar 12, 2009;
DOI: 10.1161/STROKEAHA.108.535534

Stroke
Journal of the American Heart Association

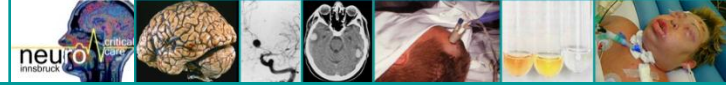
American Stroke Association
A Division of American Heart Association

neurocritical care society Neurocrit Care (2010) 12:181–187
DOI 10.1007/s12028-009-9311-z

ORIGINAL ARTICLE

Moderate Hypoglycemia is Associated With Vasospasm, Cerebral Infarction, and 3-Month Disability After Subarachnoid Hemorrhage

Andrew M. Naidech · Kimberly Levasseur · Storm Liebling · Rajeev K. Garg · Michael Shapiro · Michael L. Ault · Sherif Afifi · H. Hunt Batjer



This patient population presents many clinical challenges. Advances in our knowledge of pathophysiology and critical care management will continue to have substantial impact on patient care. Thus, the recommendations presented in this document should be reviewed on a regular basis to determine whether changes are warranted.

neurocritical care society Neurocrit Care (2011)
DOI 10.1007/s12028-

REVIEW

Critical Care Management of Patients Following Aneurysmal Subarachnoid Hemorrhage: Recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference

Michael N. Diringer · Thomas P. Bleck · J. Claude Hemphill III · David Menon · Lori Shutter · Paul Vespa · Nicolas Bruder · E. Sander Connolly Jr. · Giuseppe Citerio · Daryl Gress · Daniel Hänggi · Brian L. Hoh · Giuseppe Lanzino · Peter Le Roux · Alejandro Rabinstein · Erich Schmutzhard · Nino Stocchetti · Jose I. Suarez · Miriam Treggiari · Ming-Yuan Tseng · Mervyn D. I. Vergouwen · Stefan Wolf · Gregory Zipfel

neurocritical care society Neurocrit Care (2011) 15:257–269
DOI 10.1007/s12028-011-9598-4

REVIEW

Cardiovascular and Pulmonary Complications of Aneurysmal Subarachnoid Hemorrhage

Nicolas Bruder · Alejandro Rabinstein ·
The Participants in the International Multi-disciplinary Consensus Conference
on the Critical Care Management of Subarachnoid Hemorrhage

REVIEW

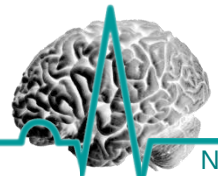
Spontaneous Subarachnoid Hemorrhage and Glucose Management

Erich Schmutzhard · Alejandro A. Rabinstein ·
The Participants in the International multi-disciplinary Consensus Conference
on the Critical care Management of Subarachnoid Hemorrhage

REVIEW

Fever Management in SAH

V. Scaravilli · G. Tinchero · G. Citerio ·
The Participants in the International Multi-disciplinary Consensus
Conference on the Critical Care Management of Subarachnoid Hemorrhage



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neurocritical care society Neurocrit Care (2011) 15:211–240
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Medical Measures to Prevent Rebleeding

Cardiopulmonary Complications

Seizures and Prophylactic Anticonvulsant Use

Monitoring Intravascular Volume Status

Managing Intravascular Volume Status

Glucose Management

Deep Venous Thrombosis Prophylaxis

Magnesium

Management of Pyrexia

Statins

Anemia and Transfusion

Delayed Cerebral Ischemia and Vasospasm

Hemodynamic Management of DCI

Endovascular Management of DCI

Delayed Neurological Deterioration

Monitoring for DCI and Triggers for Intervention

Management of Hyponatremia

Endocrine Function

High Volume Centers

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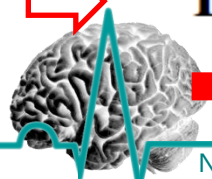

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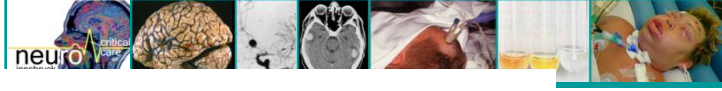

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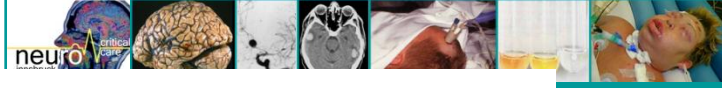

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Thank you for your attention

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Thank you for your attention

and many thanks to my coworkers:

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