

# Ischemia cerebrale dopo emorragia subaracnoidea Vasospasmo e altri nemici

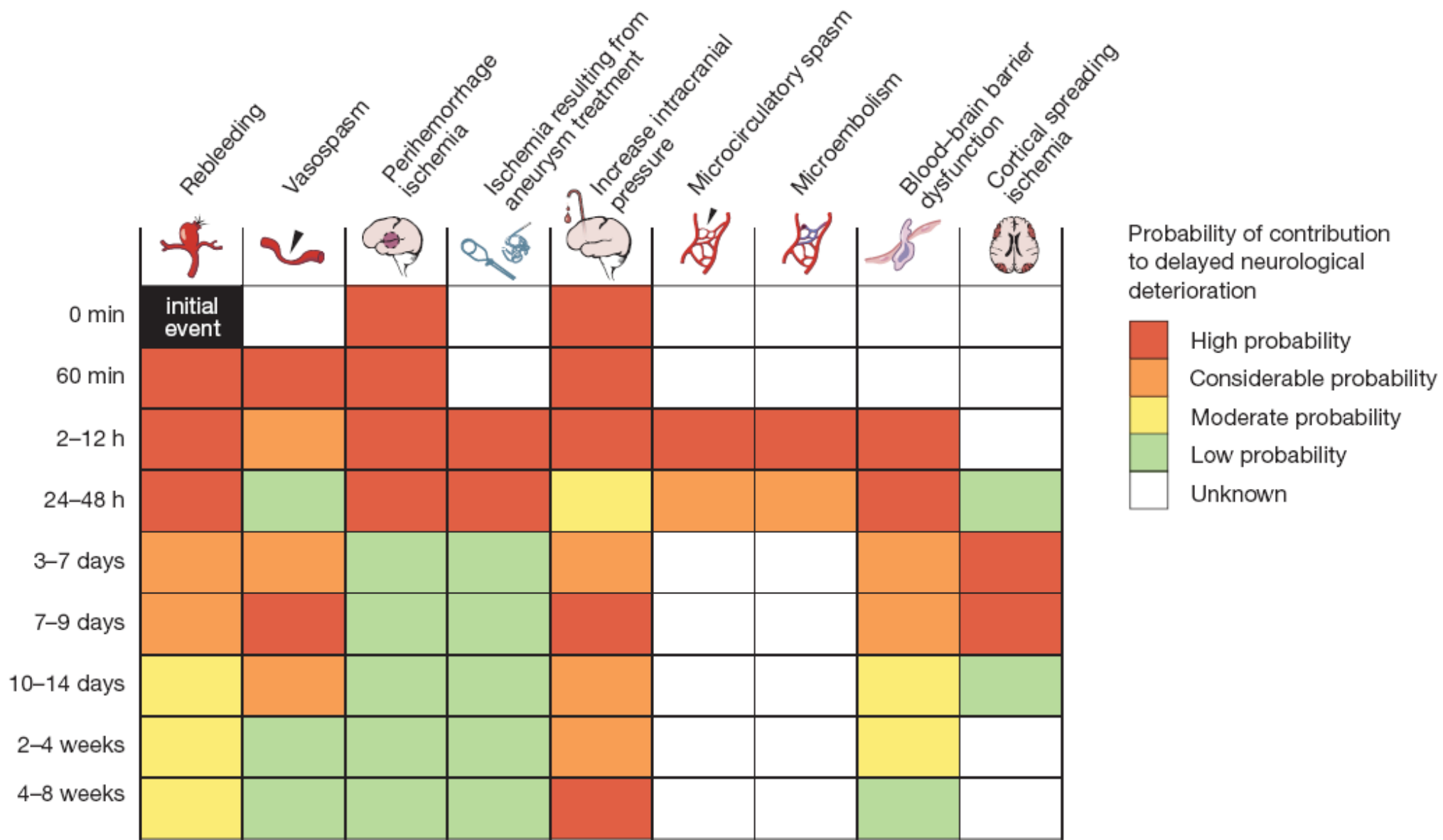


Nino Stocchetti

Milan University  
Neuroscience ICU – Ospedale  
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de Oliveira Manoel et al. *Critical Care* (2016) 20:21  
DOI 10.1186/s13054-016-1193-9



REVIEW

Open Access



# The critical care management of poor-grade subarachnoid haemorrhage

Airton Leonardo de Oliveira Manoel<sup>1,2\*</sup>, Alberto Goffi<sup>3</sup>, Tom R. Marotta<sup>1</sup>, Tom A. Schweizer<sup>2</sup>,  
Simon Abrahamson<sup>1</sup> and R. Loch Macdonald<sup>1,2</sup>

**Definition of Delayed Cerebral Ischemia After Aneurysmal  
Subarachnoid Hemorrhage as an Outcome Event in Clinical  
Trials and Observational Studies**

**Proposal of a Multidisciplinary Research Group**

Mervyn D.I. Vergouwen, MD, PhD; Marinus Vermeulen, MD, PhD;  
Jan van Gijn, MD, FRCP, FRCP(Edin); Gabriel J.E. Rinkel, MD; Eelco F. Wijdicks, MD, PhD;  
J. Paul Muizelaar, MD, PhD; A. David Mendelow, MD, PhD; Seppo Juvela, MD, PhD;  
Howard Yonas, MD; Karel G. Terbrugge, MD, FRCPC; R. Loch Macdonald, MD, PhD;  
Michael N. Diringer, MD; Joseph P. Broderick, MD; Jens P. Dreier, MD, PhD;  
Yvo B.W.E.M. Roos, MD, PhD

**Focal neurological impairment** (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or  
a decrease of at least 2 points on GCS

**Lasting for at least 1 hour**  
**not apparent immediately after aneurysm occlusion**

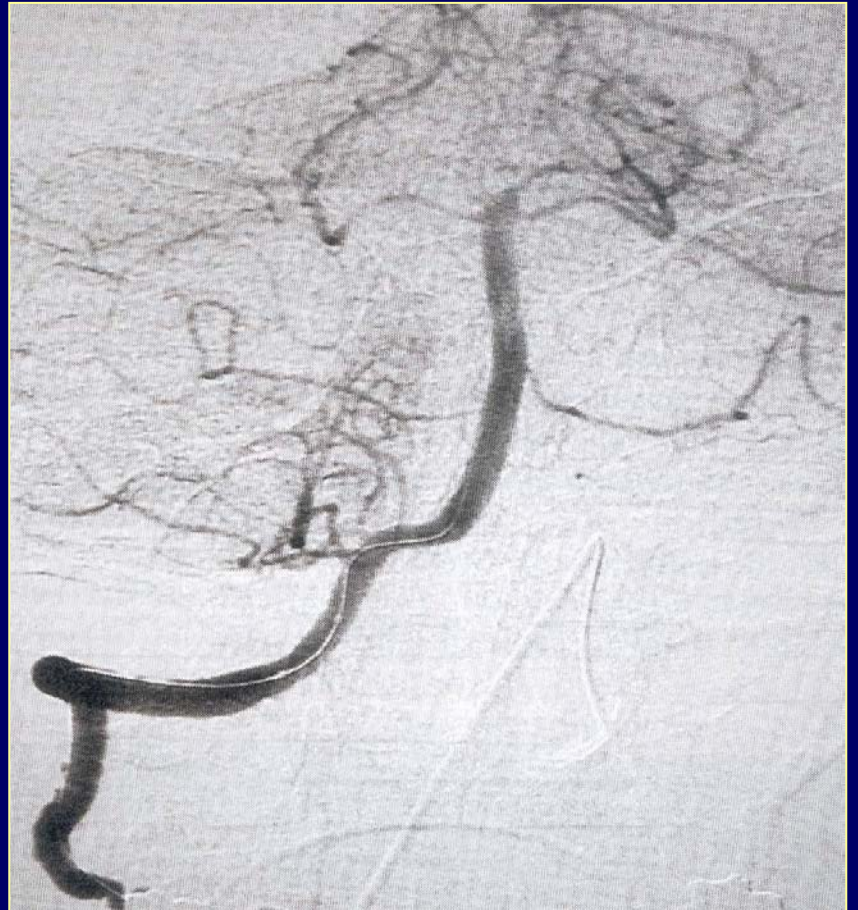
**cannot be attributed to other causes** by means of clinical assessment, CT or MRI scanning of the  
brain, and appropriate laboratory studies



Narrowing



< Flow





Narrowing



< Flow

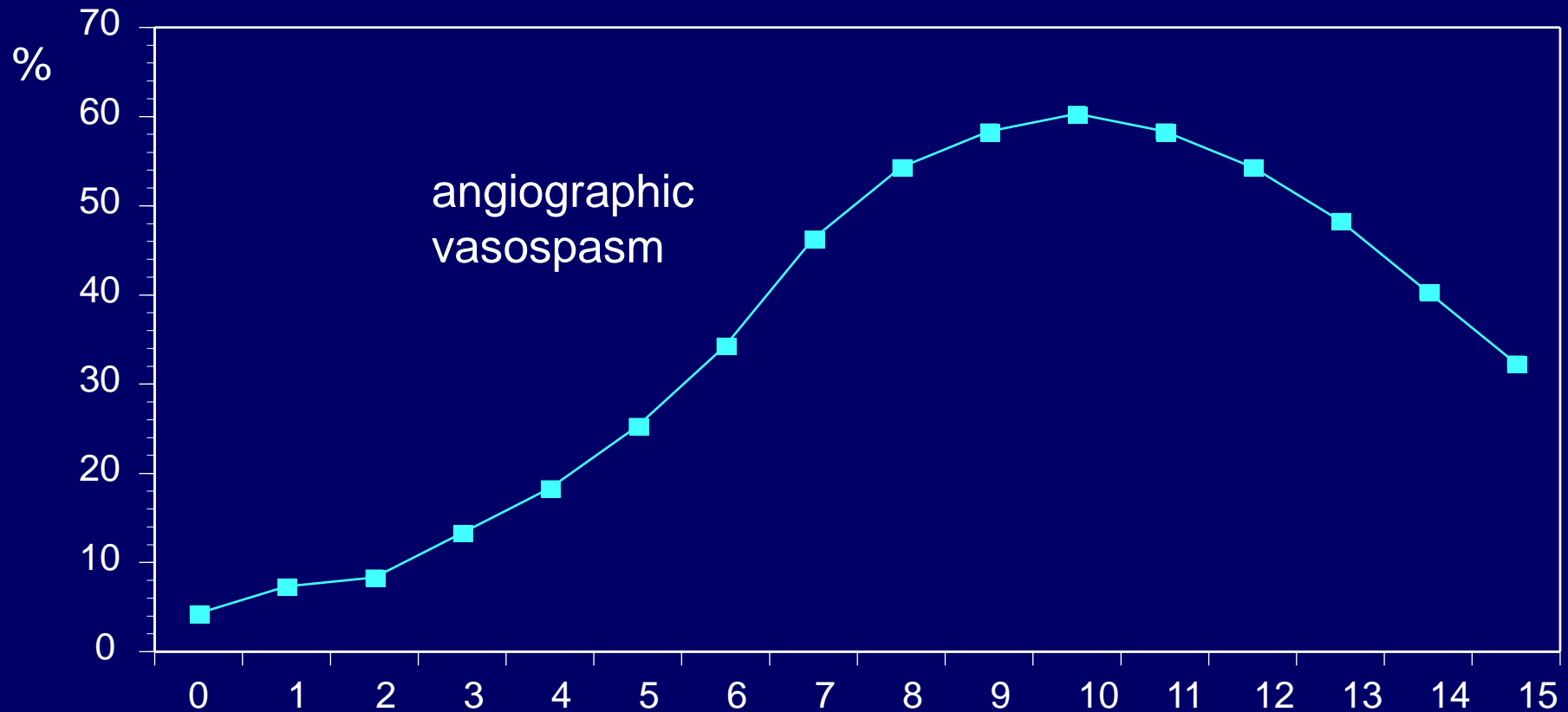


Inadequate  
delivery



# Cumulative incidence: AGF VSP

■ up to 70%

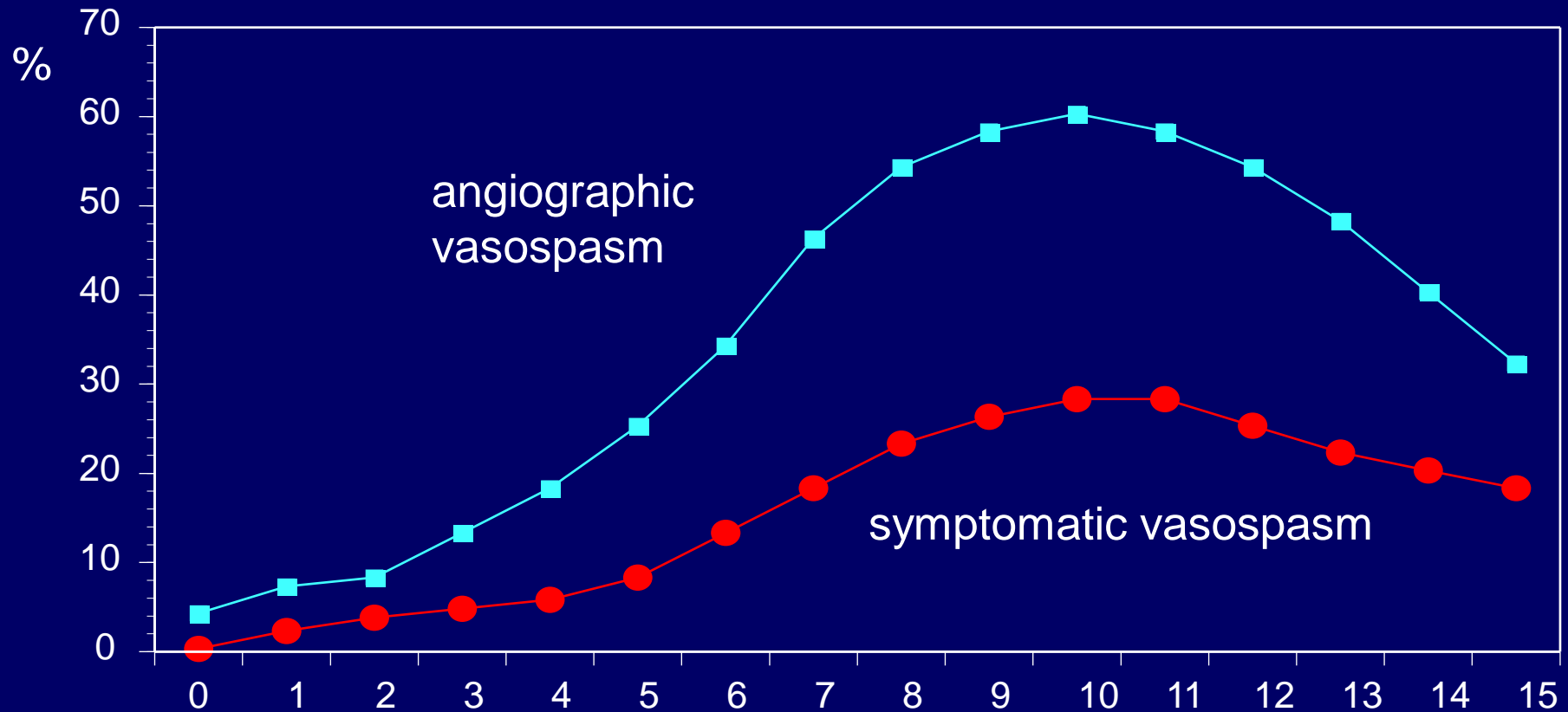







# Cumulative incidence: AGF VSP

- up to 70%
- up to 40%





## **Relationship Between Angiographic Vasospasm and Regional Hypoperfusion in Aneurysmal Subarachnoid Hemorrhage**

Rajat Dhar, MD; Michael T. Scalfani, MSCI; Spiros Blackburn, MD; Allyson R. Zazulia, MD;  
Tom Videen, PhD; Michael Diringer, MD

27 patients by PET and AGF

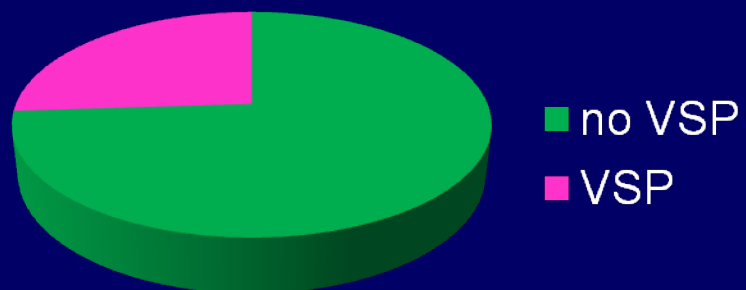
Median 7 days after SAH

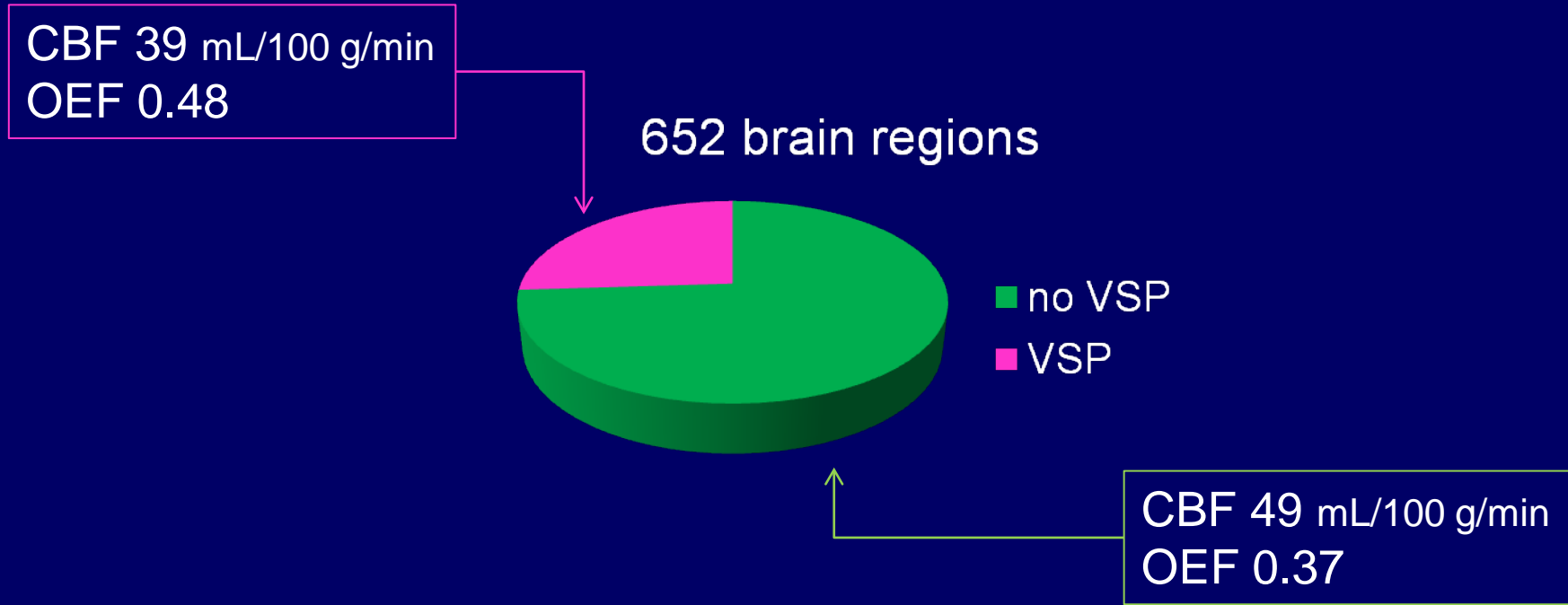
700 brain regions

48 excluded (infarct, haematoma, etc.)



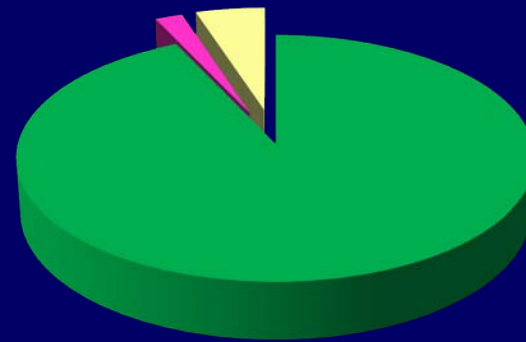
652 brain regions







652 brain regions



- no hypoperfusion
- hypoperfusion no VSP
- hypoperfusion and VSP

10 patients with neurological deficit  
7 with VSP  
3 without



Narrowing



< Flow



microcirculation



Inadequate  
delivery



OPEN

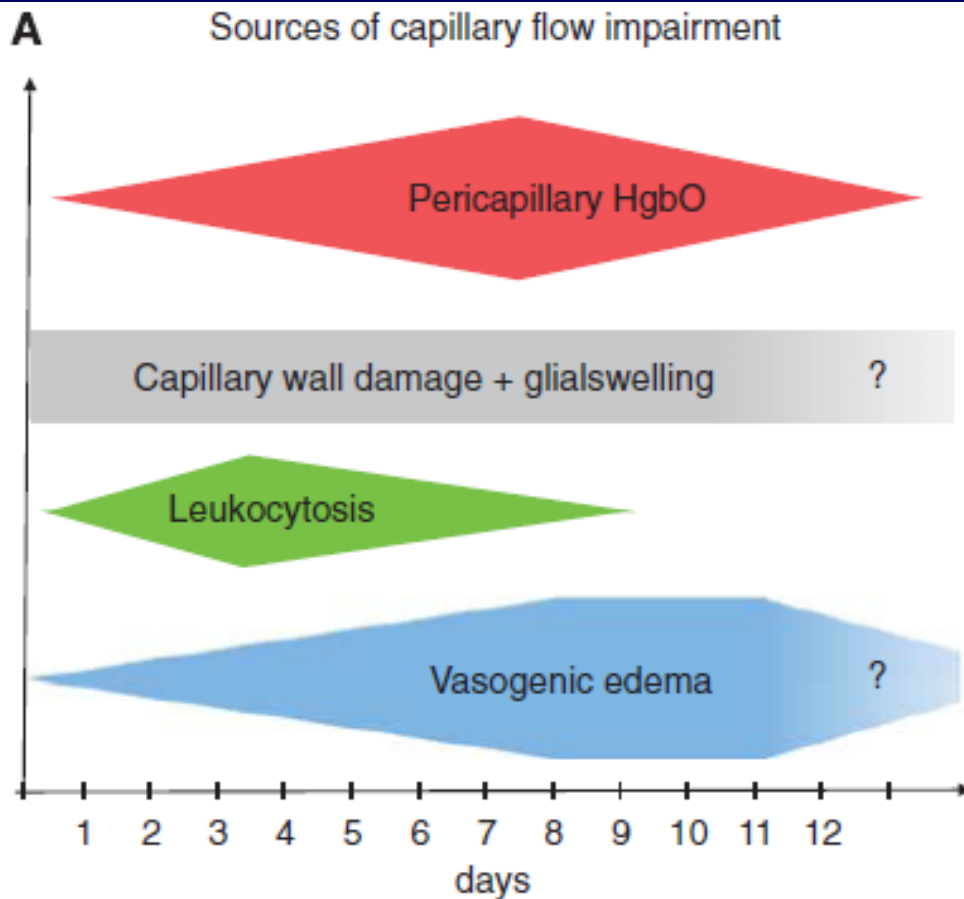
Journal of Cerebral Blood Flow & Metabolism (2013) 33, 1825–1837  
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[www.jcbfm.com](http://www.jcbfm.com)

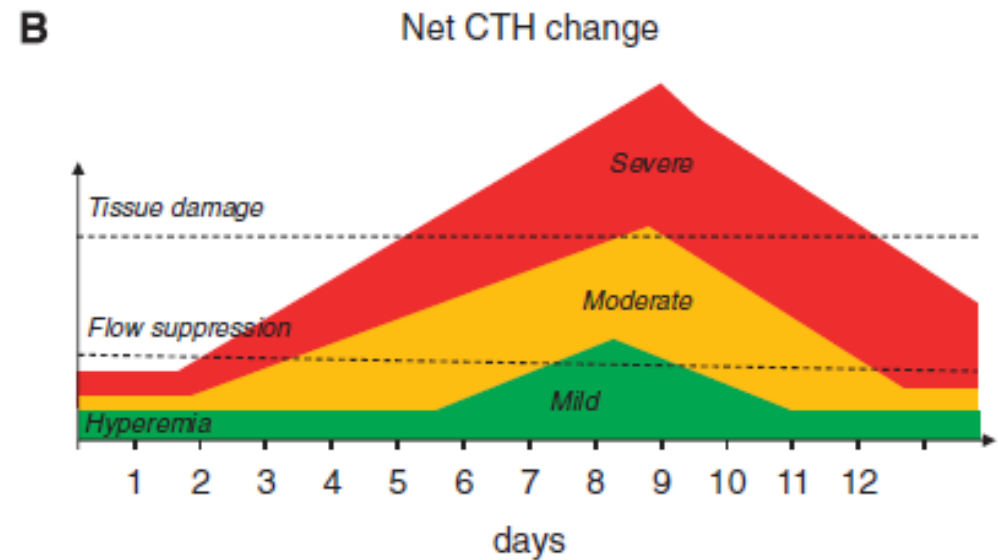
**REVIEW ARTICLE**

# The role of the microcirculation in delayed cerebral ischemia and chronic degenerative changes after subarachnoid hemorrhage

Leif Østergaard<sup>1,2</sup>, Rasmus Aamand<sup>2</sup>, Sanja Karabegovic<sup>1</sup>, Anna Tietze<sup>1,2</sup>, Jakob Udby Blicher<sup>2,3</sup>, Irene Klærke Mikkelsen<sup>2</sup>, Nina Kerting Iversen<sup>2</sup>, Niels Secher<sup>4</sup>, Thorbjørn Søndergaard Engedal<sup>1,2</sup>, Mariam Anzabi<sup>2</sup>, Eugenio Gutierrez Jimenez<sup>2</sup>, Changsi Cai<sup>2</sup>, Klaus Ulrik Koch<sup>4</sup>, Erhard Trillingsgaard Næss-Schmidt<sup>3</sup>, Annette Obel<sup>1</sup>, Niels Juul<sup>4</sup>, Mads Rasmussen<sup>4</sup> and Jens Christian Hedemann Sørensen<sup>5</sup>



Capillary Transit time Heterogeneity





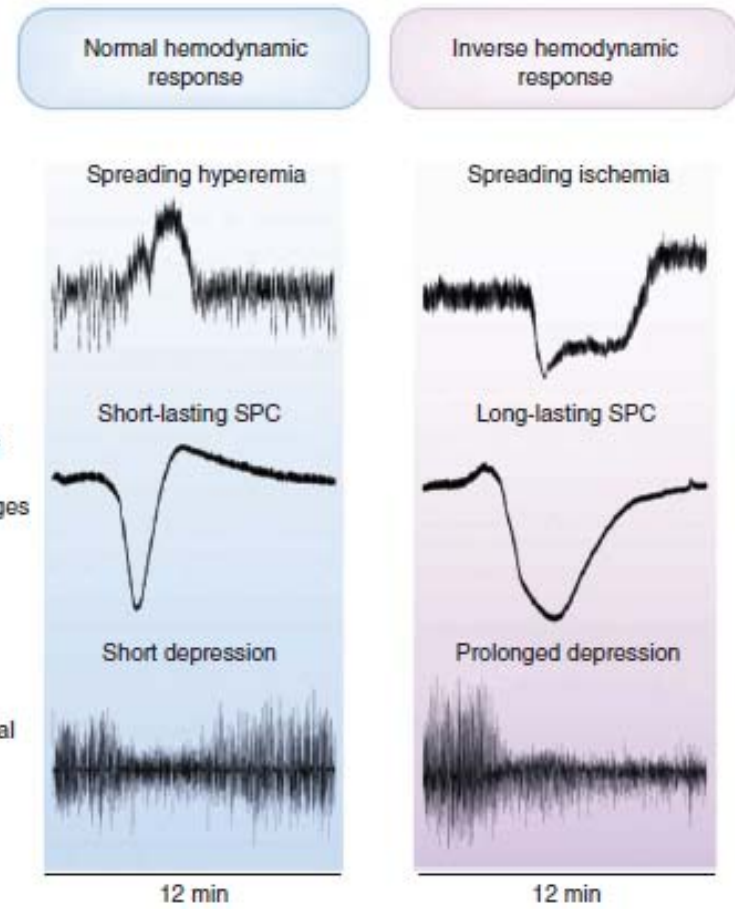
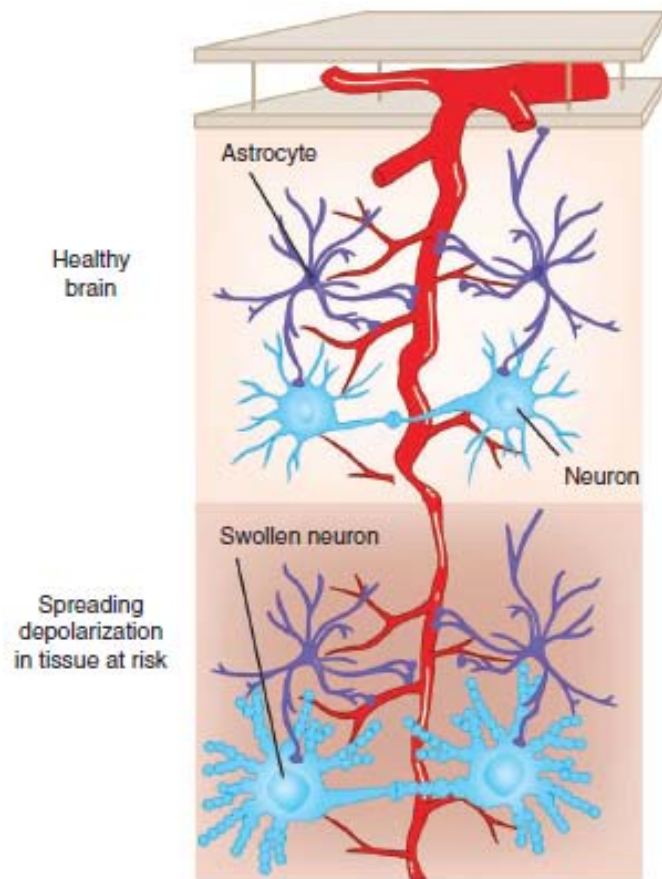


nature  
medicine

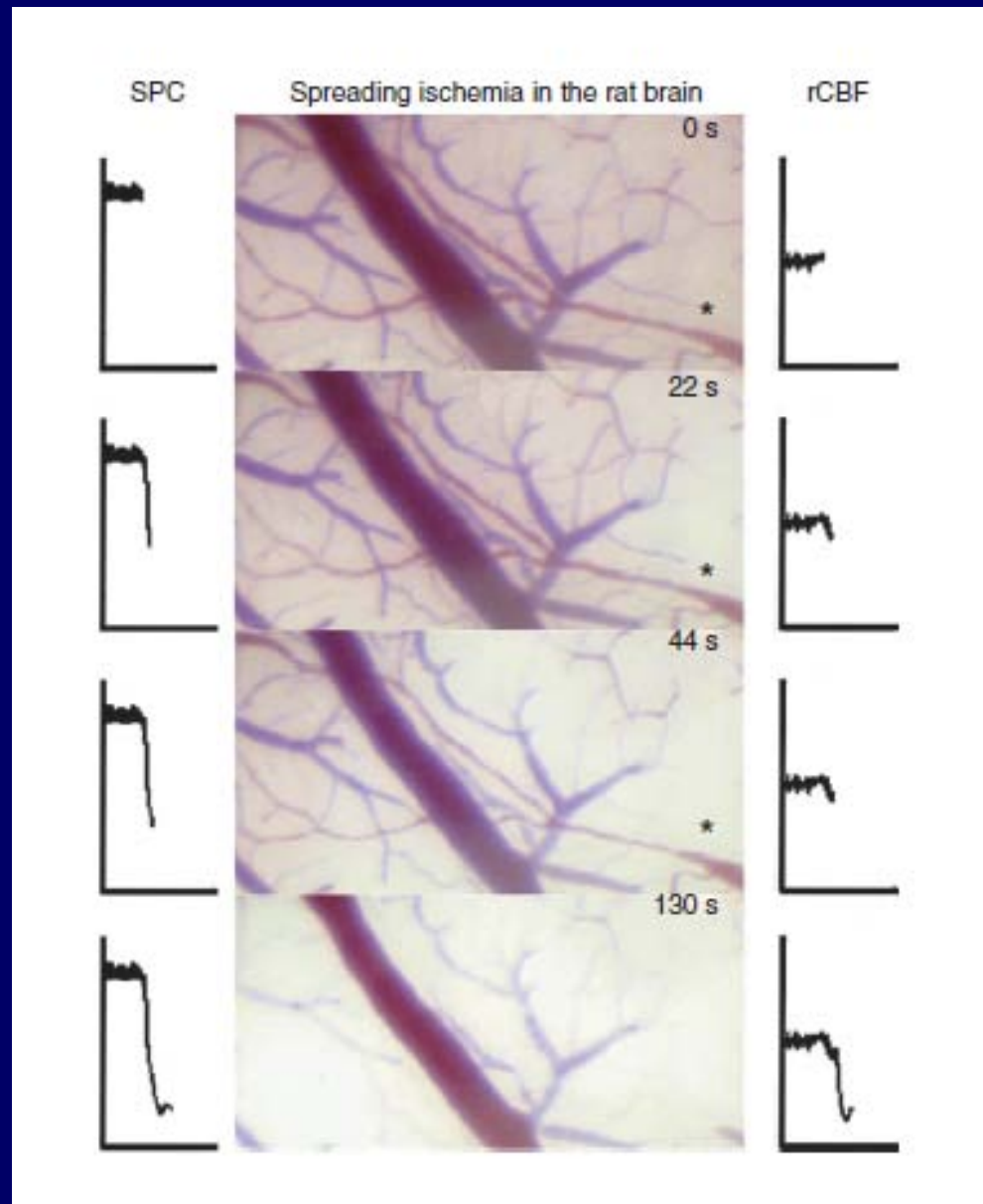
**REVIEW**

# The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease

Jens P Dreier

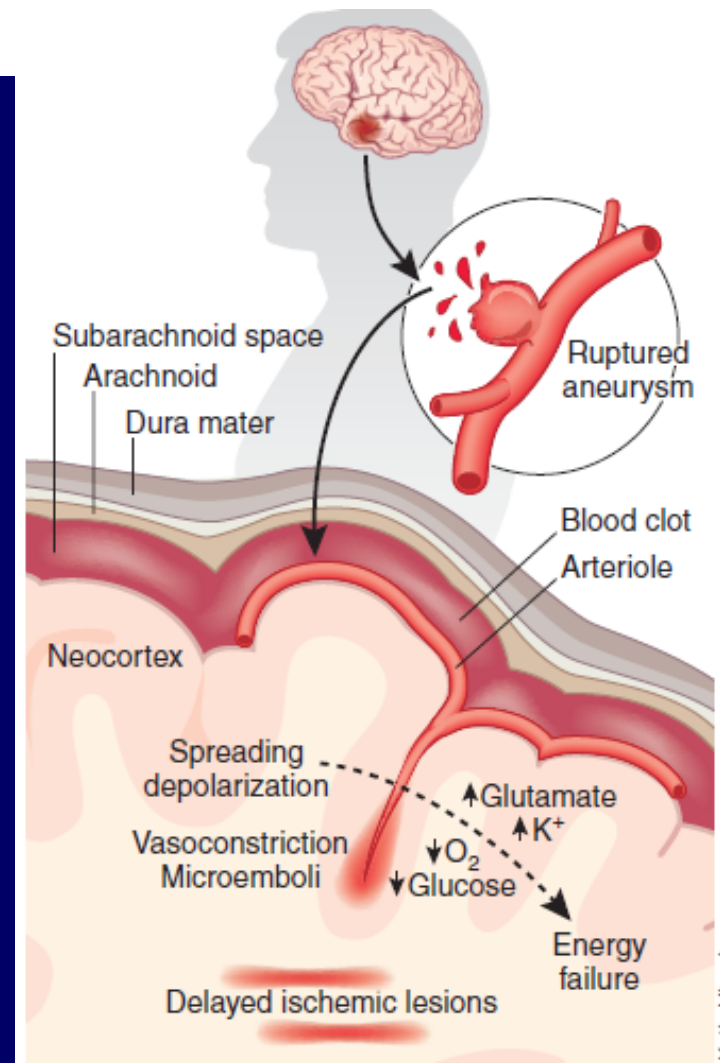


SPC: slow potential change



# Killer waves of depolarization in subarachnoid bleed

Costantino Iadecola



Feature Article Commentary

# **Cortical spreading ischemia in the absence of proximal vasospasm after aneurysmal subarachnoid hemorrhage: evidence for a dual mechanism of delayed cerebral ischemia**

Anthony J Strong<sup>1</sup> and R Loch Macdonald<sup>2</sup>

<sup>1</sup>*King's College London, Department of Clinical Neuroscience, Institute of Psychiatry, London, UK;*

<sup>2</sup>*Division of Neurosurgery, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada*



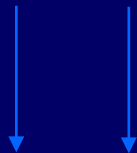
Narrowing



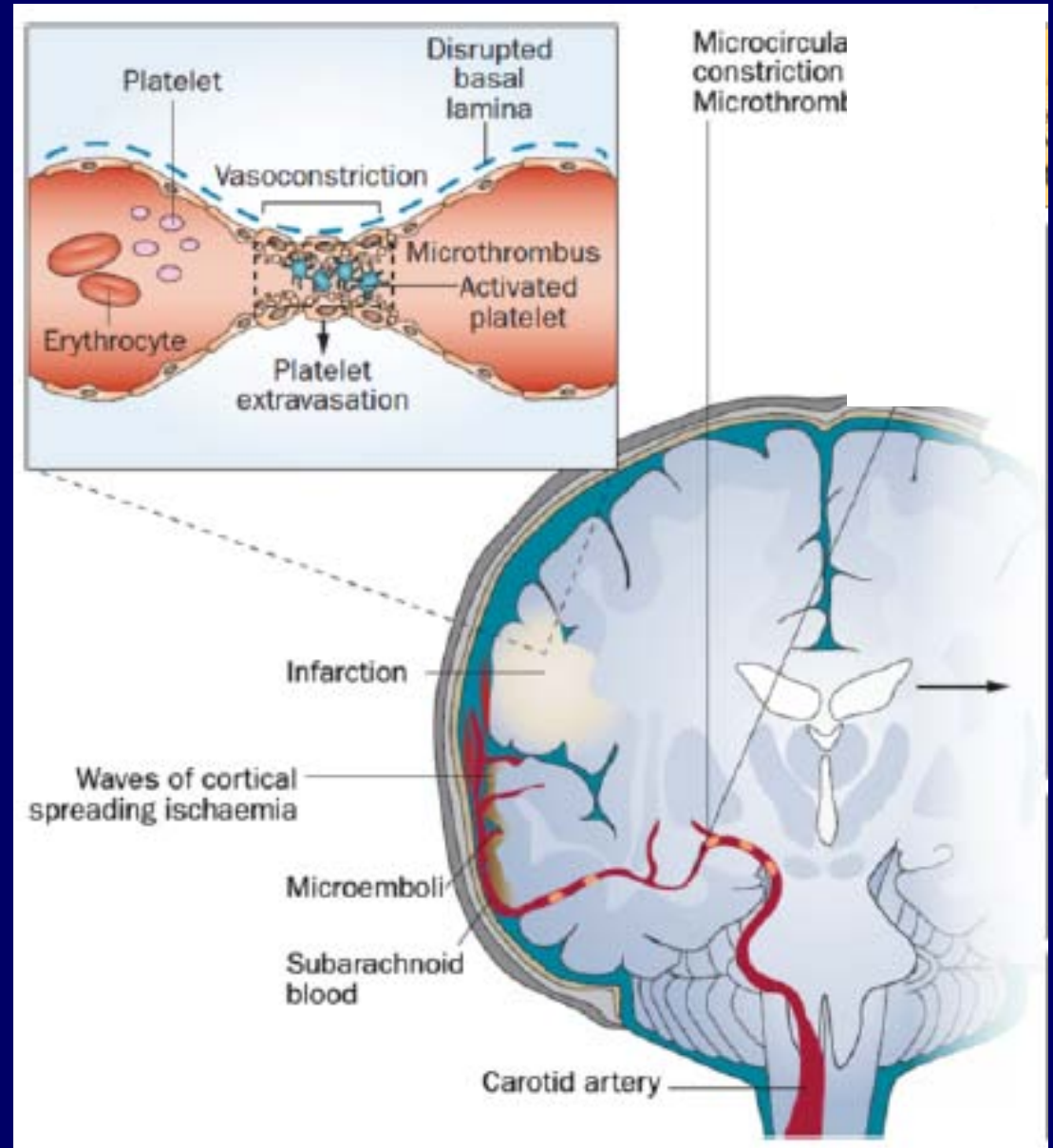
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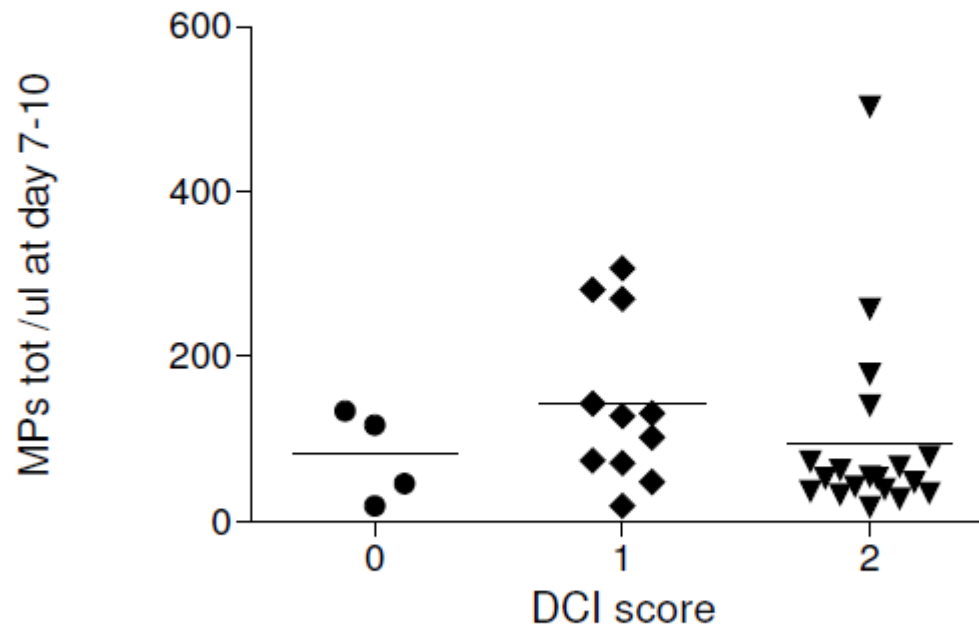


microcirculation



Inadequate delivery







Narrowing



< Flow



microcirculation



Inadequate delivery

Prevent VSP

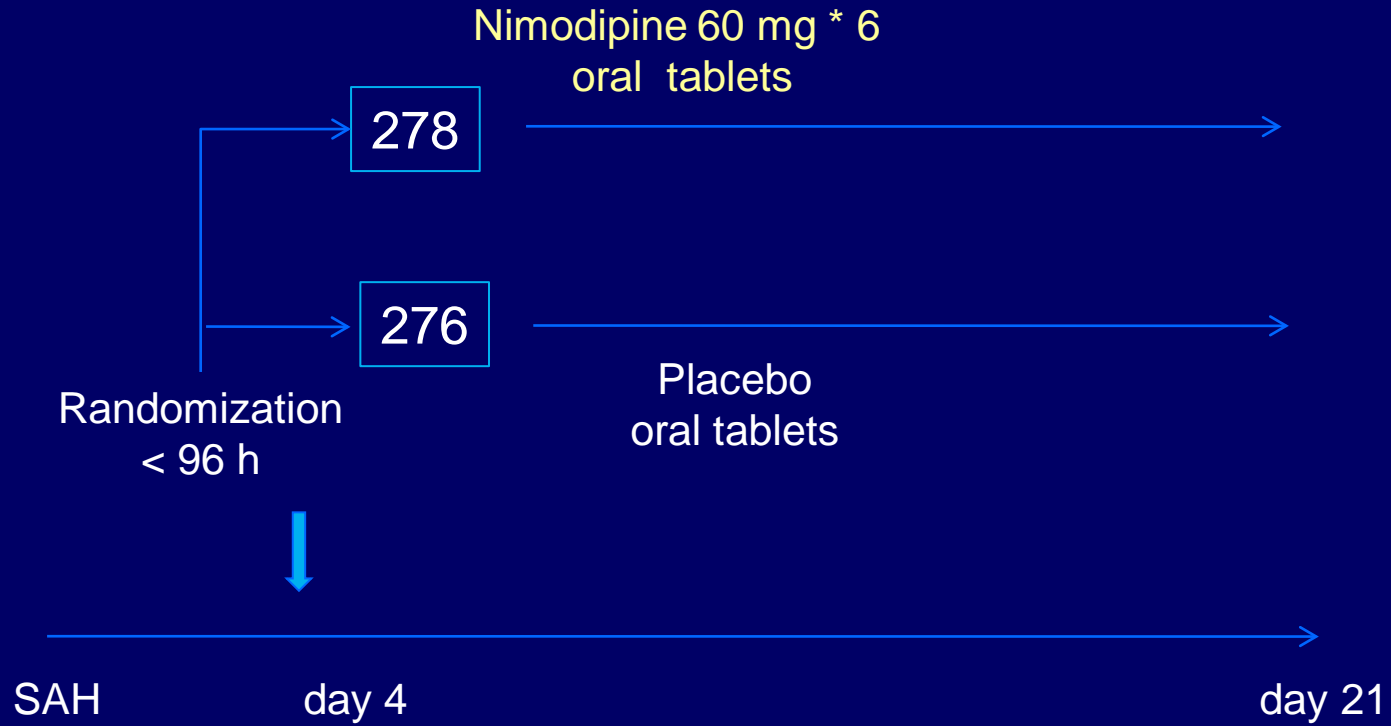
Infarct

VSP



**Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial**

J D Pickard, G D Murray, R Illingworth, M D M Shaw, G M Teasdale, P M Foy, P R D Humphrey, D A Lang, R Nelson, P Richards, J Sinar, S Bailey, A Skene



4 centers  
N = 554



TABLE II—*Effect of nimodipine on incidence of cerebral infarction and outcome after subarachnoid haemorrhage. Values are numbers (percentages) of patients unless stated otherwise*

	Patients taking nimodipine (n=278)	Patients taking placebo (n=276)	Relative reduction (%)	95% Confidence interval	Significance (p value)
Cerebral infarct	61 (22)	92 (33)	34	13 to 50	0.003 ( $\chi^2 = 8.99$ ; df=1)
Poor outcome	55 (20)	91 (33)	40	20 to 55	<0.001 ( $\chi^2 = 12.41$ ; df=1)
Rebleed	25 (9)	38 (14)	35	-5 to 59	0.077 ( $\chi^2 = 3.13$ ; df=1)

No effect on VSP incidence



## Hunt and Hess

1. Asymptomatic or minimal headache, slight nuchal rigidity
2. Moderate-severe headache, muchal rigidity, no deficits other than cranial nerves palsy
3. Drowsy, confusion or mild focal deficit
4. Stupor, moderate-severe hemiparesis, decerebrate rigidity and vegetative disturbances
5. Deep coma, decerebrate rigidity, moribund appearance

## World Federation of Neurol Surgeons

1. GCS 15
2. GCS 13-14
3. GCS 13-14 with motor deficit
4. GCS 7-12 with or without motor deficit
5. GCS 3-6 with or without motor deficit



	Nimodipine	Placebo
	276	278
I	8	12
II	168	159
III	76	72
IV	19	25
V	7	8

“The protocol allowed for adjustment of the dose if hypotension occurred, but this was not found to be necessary .. Patients were monitored clinically ”

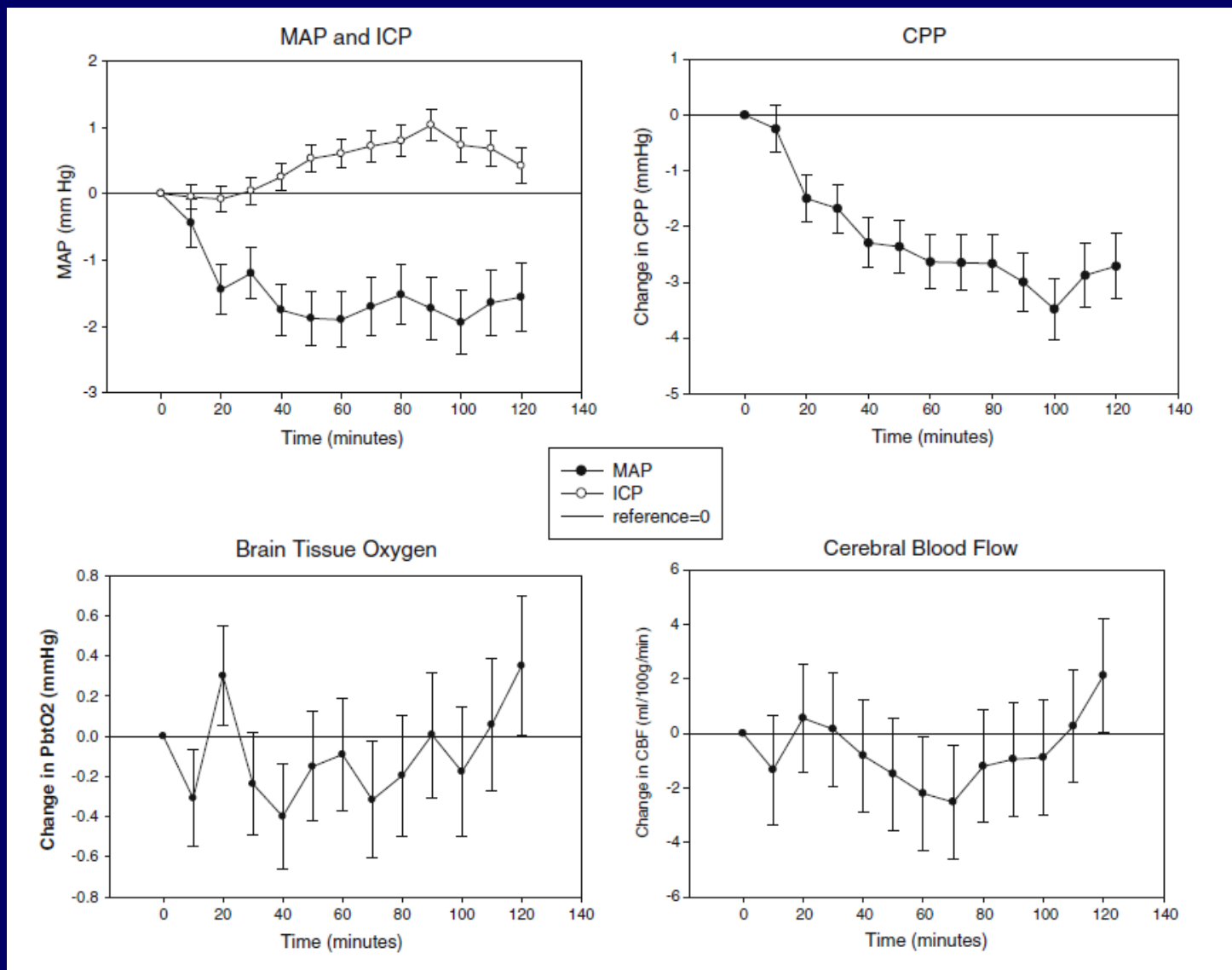


ORIGINAL ARTICLE

## **Acute Effects of Nimodipine on Cerebral Vasculature and Brain Metabolism in High Grade Subarachnoid Hemorrhage Patients**

**H. Alex Choi · Sang-Bae Ko · Huahiou Chen · Emily Gilmore · Amanda M. Carpenter ·  
Danielle Lee · Jan Claassen · Stephan A. Mayer · J. Michael Schmidt ·  
Kiwon Lee · E. Sander Connelly · Myunghee Paik · Neeraj Badjatia**

16 pts



Out of a total of 663 Nimodipine doses, 365 (55%) resulted in a MAP decrease



Narrowing



< Flow



Inadequate delivery

Prevent VSP

Infarct

VSP

Implants

Statins

Clazosentan

Magnesium



## Efficacy of controlled-release papaverine pellets in preventing symptomatic cerebral vasospasm

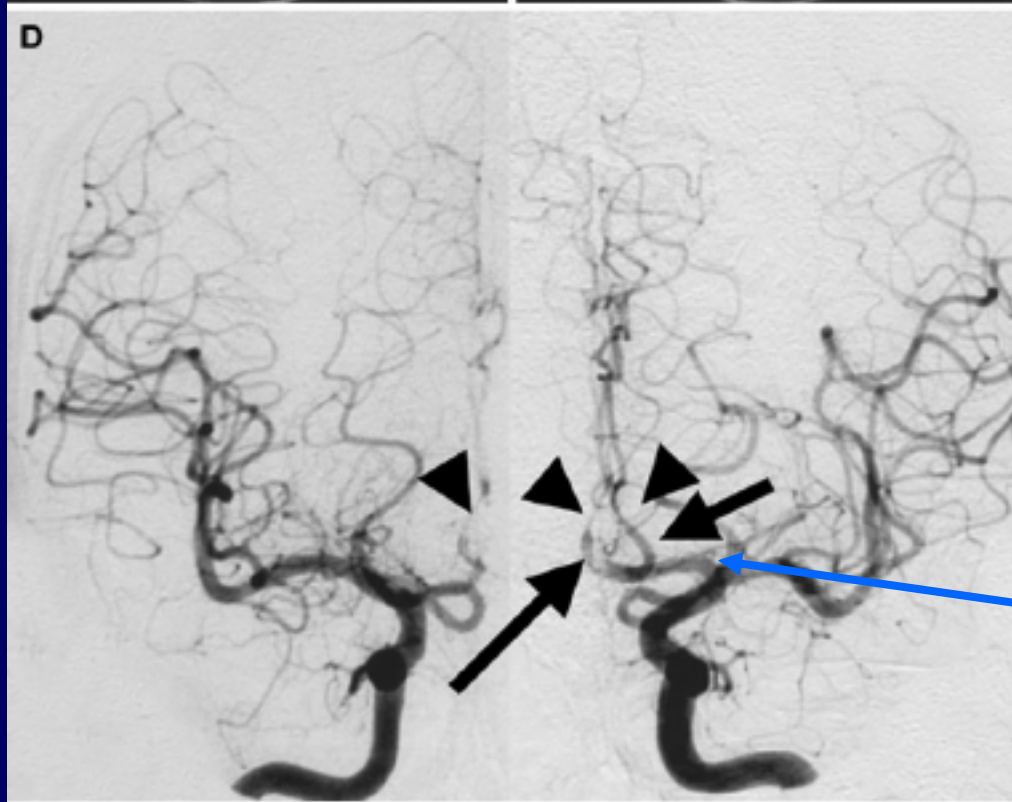
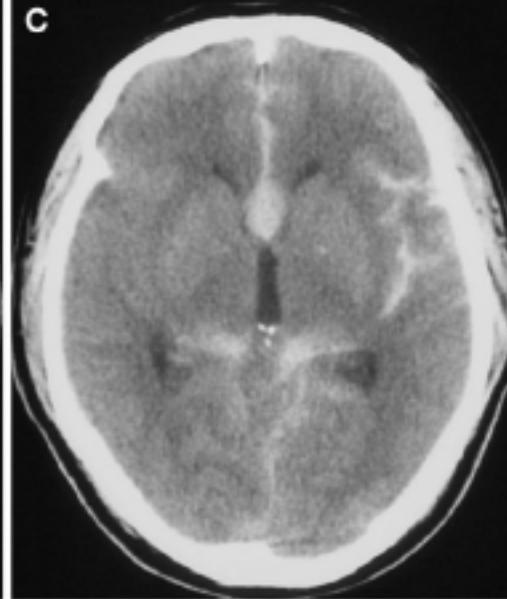
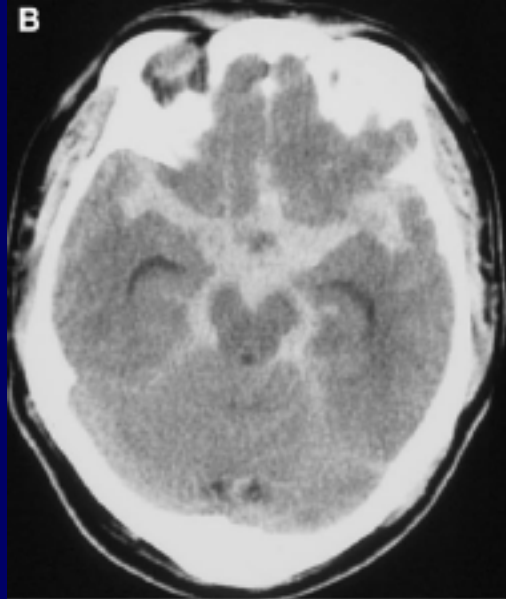
**TAYFUN DALBASTI, M.D., MURAT KARABIYIKOGLU, M.D., NURCAN OZDAMAR, M.D.,  
NEZIH OKTAR, M.D., AND SEDAT CAGLI, M.D.**

*Department of Neurosurgery, University of Ege, School of Medicine, Izmir, Turkey*



## CLINICAL STUDIES

# APPLICATION OF NICARDIPINE PROLONGED-RELEASE IMPLANTS: ANALYSIS OF 97 CONSECUTIVE PATIENTS WITH ACUTE SUBARACHNOID HEMORRHAGE

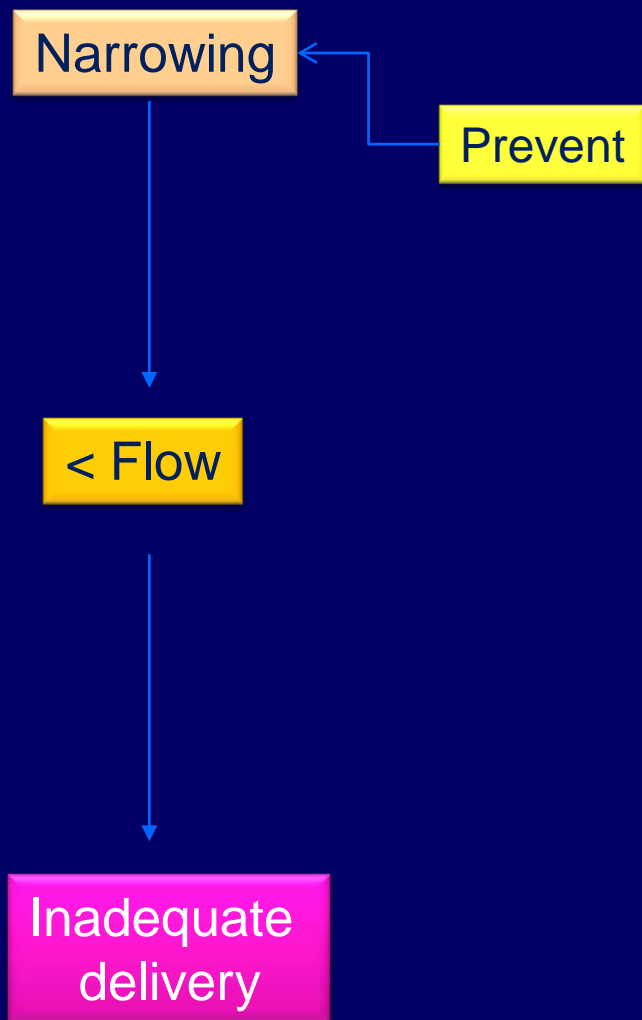


Implants



Implants

Statins



# Statins

## Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Stroke  
Association<sup>SM</sup>

A Division of American  
Heart Association



**'Yes' or 'No' to Routine Statins After Subarachnoid Hemorrhage to Prevent  
Delayed Cerebral Ischaemia, Vasospasm, and Death?: A Cautionary Tale of 2  
Meta-Analyses**  
Peter Sandercock

Clazosentan an endothelin receptor antagonist designed to inhibit endothelin-mediated cerebral vasospasm

Stroke


JOURNAL OF THE AMERICAN HEART ASSOCIATION



American Heart Association | American Stroke Association<sup>®</sup>

**Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage (CONSCIOUS-1): Randomized, Double-Blind, Placebo-Controlled Phase 2 Dose-Finding Trial**

R. Loch Macdonald, Neal F. Kassell, Stephan Mayer, Daniel Ruefenacht, Peter Schmiedek, Stephan Weidauer, Aline Frey, Sebastien Roux and Alberto Pasqualin





Moderate or severe vasospasm was reduced from 66% to 23% in the 15 mg/h Clazosentan group (risk reduction, 65%; 95% CI, 47% to 78%;  $P < 0.0001$ )

No significant effects on secondary end points

Clazosentan was associated with increased rates of pulmonary complications, hypotension, and anemia

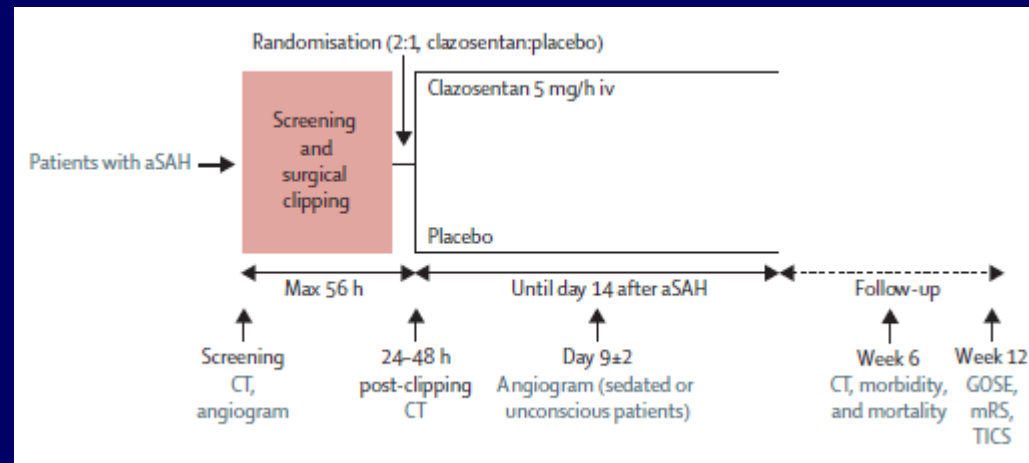
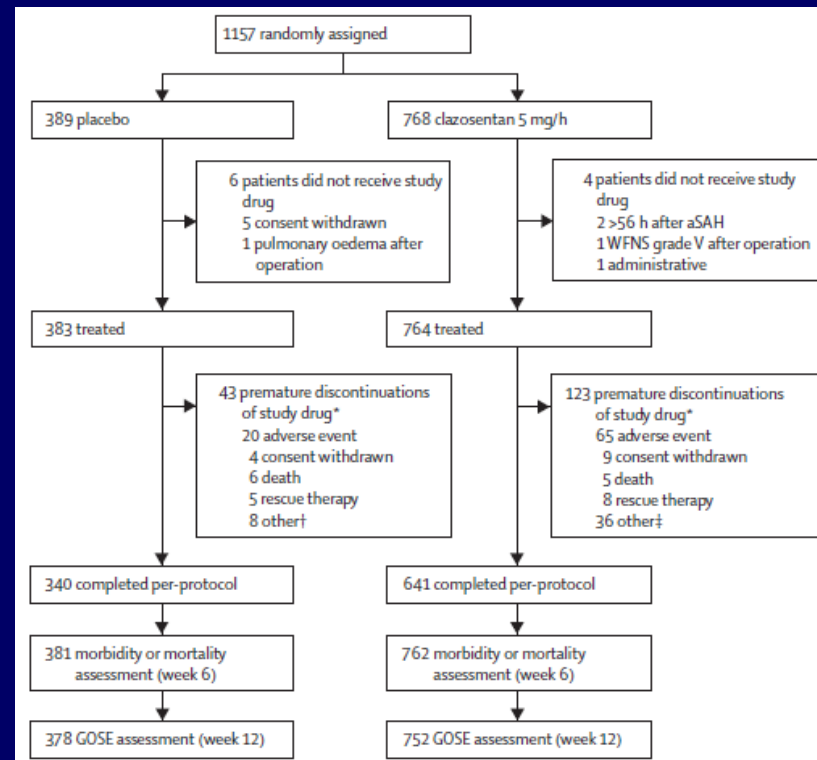


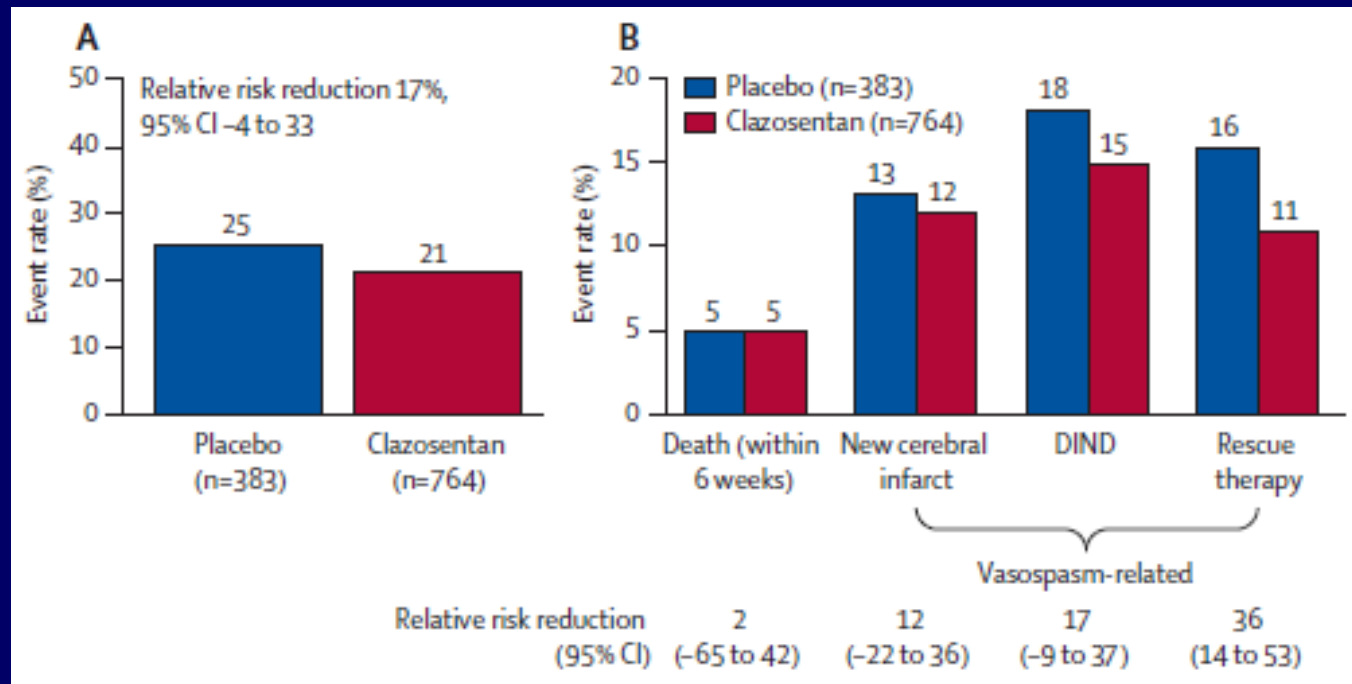
## Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: a randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2)

Dr R Loch Macdonald, MD  , Randall T Higashida, MD, Emanuela Keller, MD, Stephan A Mayer, MD, Andy Molyneux, MD, Andreas Raabe, MD, Peter Vajkoczy, MD, Isabel Wanke, MD, Doris Bach, MSc, Aline Frey, PharmD, Angelina Marr, BSc Pharm, Sébastien Roux, MD, Neal Kassell, MD

Published Online: 02 June 2011







## Magnesium infusion for vasospasm prophylaxis after subarachnoid hemorrhage

**MARTINA STIPPLER, M.D., ELIZABETH CRAGO, R.N., M.S.N., ELAD I. LEVY, M.D.,  
MARY E. KERR, R.N., PH.D., HOWARD YONAS, M.D., MICHAEL B. HOROWITZ, M.D.,  
AND AMIN KASSAM, M.D.**

*Departments of Neurological Surgery and Acute and Tertiary Nursing, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; Department of Neurosurgery and Toshiba Stroke Research Center, State University of New York at Buffalo, New York; and Division of Surgery, Department of Neurosurgery, University of New Mexico Health Sciences Center, Albuquerque, New Mexico*



38 patients with continuous MgSO<sub>4</sub> infusion were matched for age, race, sex, treatment option, Fisher grade, and Hunt and Hess grade to 38 historical control individuals

significant reduction in vasospasm and a trend toward improved outcome

when continuous MgSO<sub>4</sub> therapy was initiated within 48 hours after aneurysm rupture



# **Magnesium Sulfate in Aneurysmal Subarachnoid Hemorrhage**

## **A Randomized Controlled Trial**

Walter M. van den Bergh; on behalf of the MASH Study Group



	Total n=283	Intention to Treat n=283		On Treatment n=249	
		Magnesium	Placebo	Magnesium	Placebo
Baseline data					
No. randomized	283	139	144	122	127

	RR (95% CI)	NNT
Primary outcome		
DCI*	0.66 (0.38–1.14)‡	14 (35 NNTH to 6 NNTB)
Secondary outcomes		
New hypodensities on CT*	1.04 (0.79–1.37)	-
Poor outcome†	0.77 (0.54–1.09)	12 (37 NNTH to 5 NNTB)
Excellent outcome‡	3.4 (1.3–8.9)	11 (7 NNTB to 43 NNTB)



Narrowing



< Flow



microcirculation



Inadequate  
delivery

Prevent VSP

Detect VSP

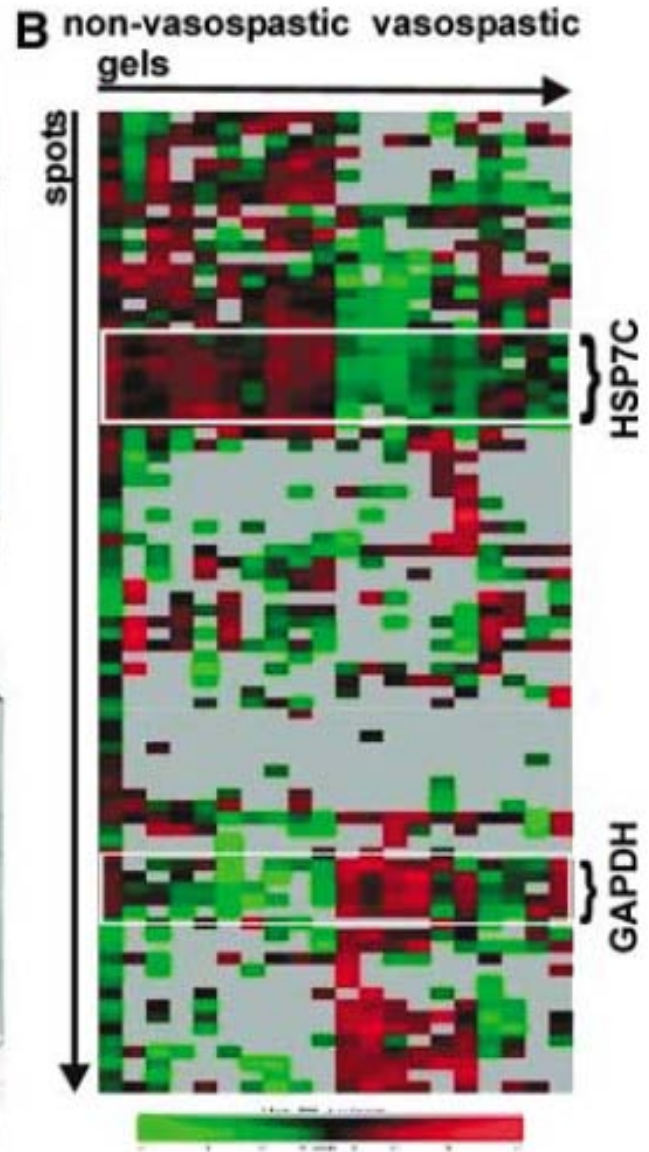
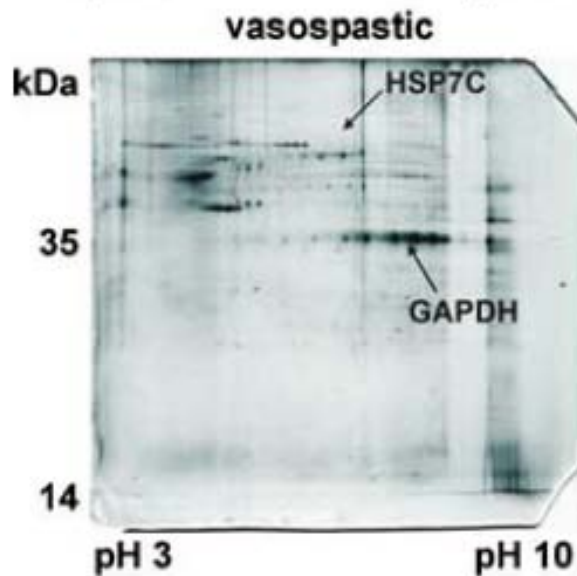
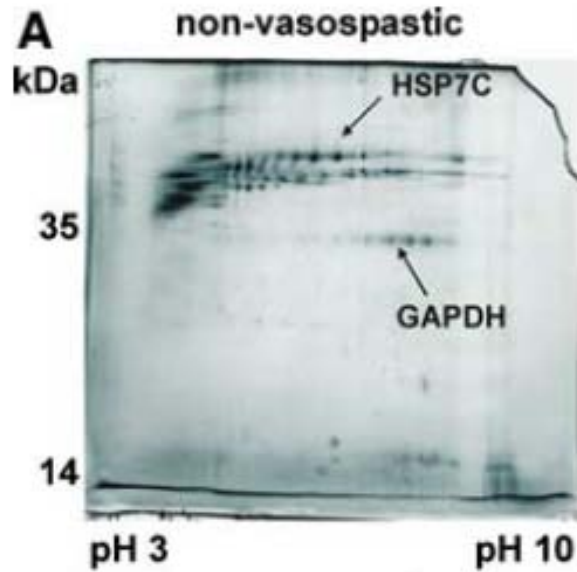
# Identification of early markers for symptomatic vasospasm in human cerebral microdialysate after subarachnoid hemorrhage: Preliminary results of a proteome-wide screening

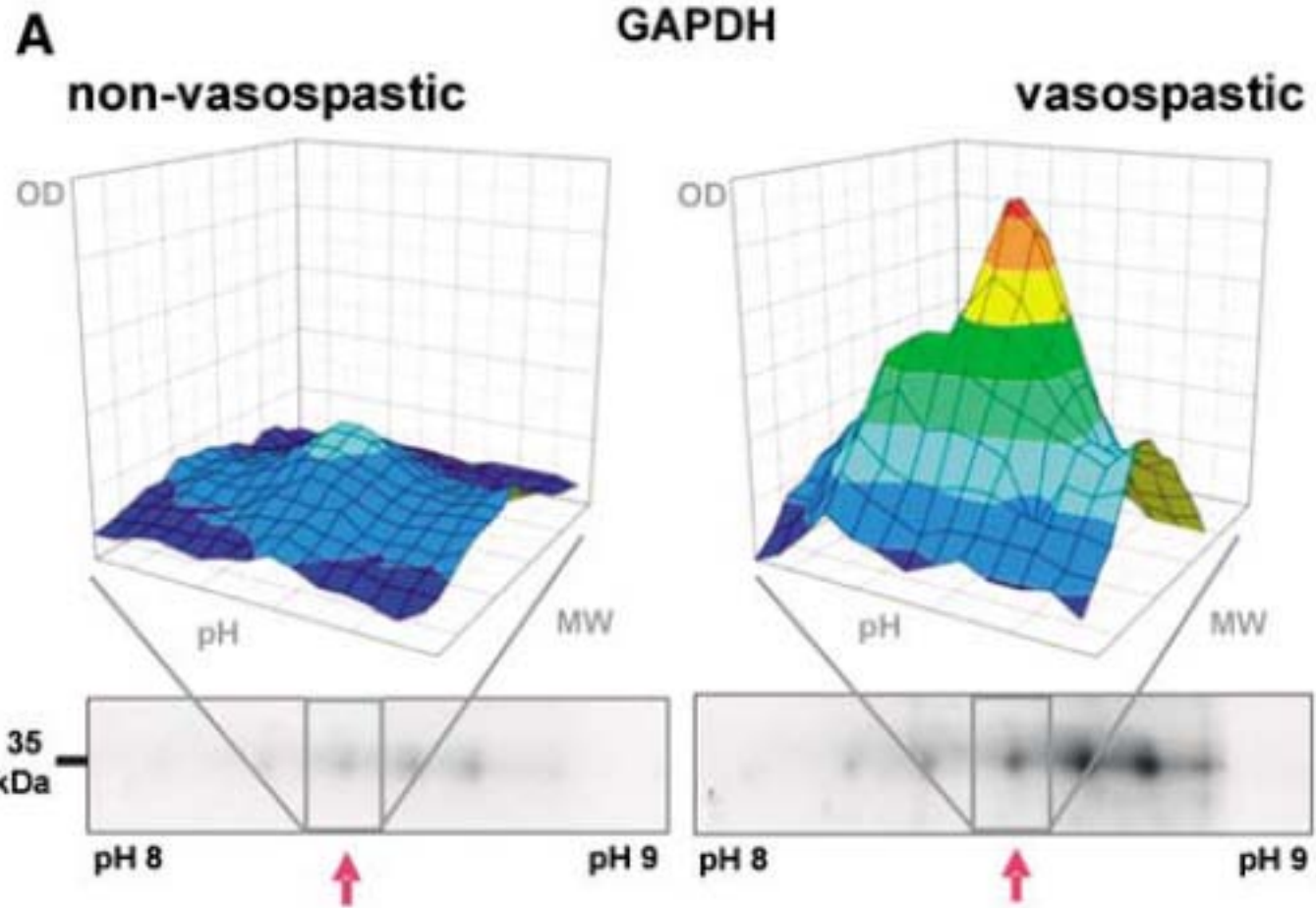
Martin H Maurer<sup>1,3</sup>, Daniel Haux<sup>2,3</sup>, Oliver W Sakowitz<sup>2</sup>, Andreas W Unterberg<sup>2</sup> and Wolfgang Kuschinsky<sup>1</sup>

<sup>1</sup>*Department of Physiology and Pathophysiology, University of Heidelberg, Heidelberg, Germany;*

<sup>2</sup>*Department of Neurosurgery, University of Heidelberg, Heidelberg, Germany*

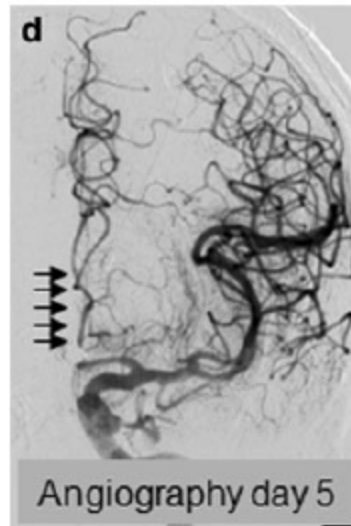
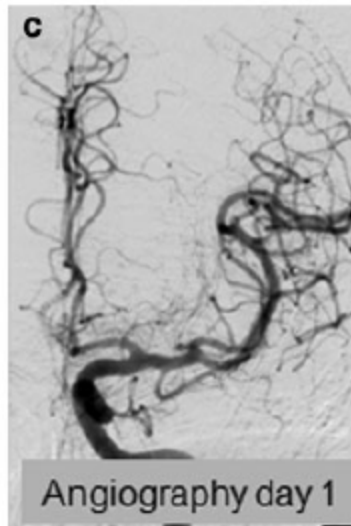
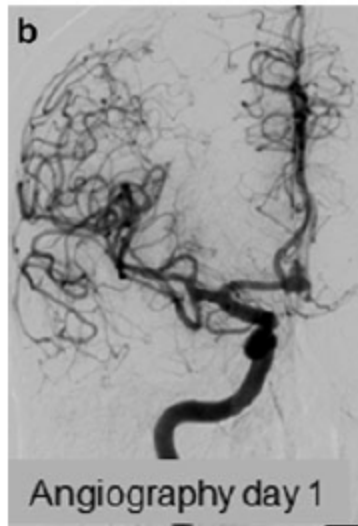
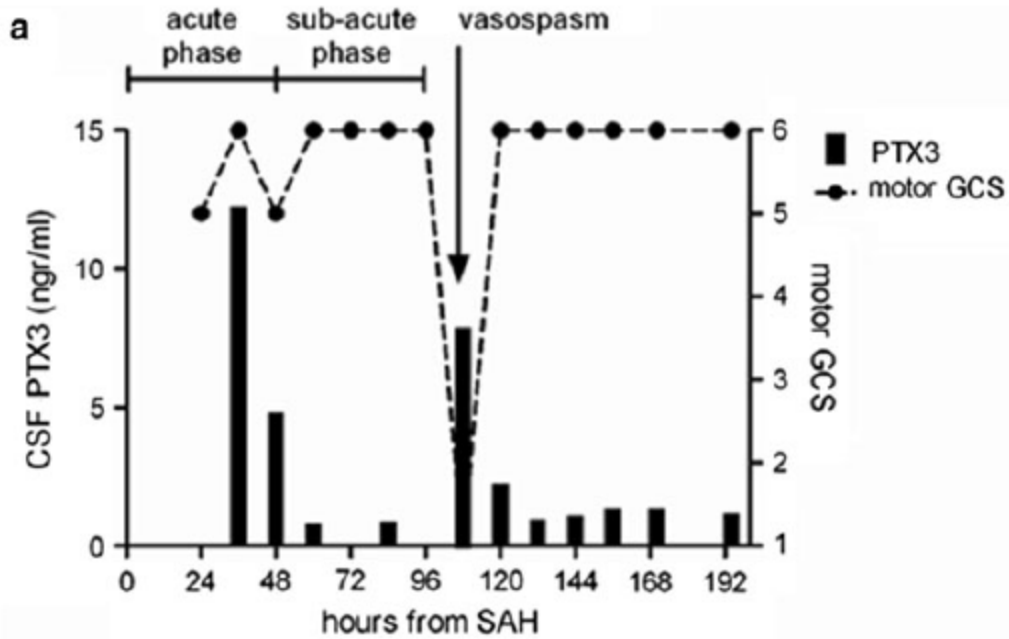







Elisa R. Zanier  
Giovanna Brandi  
Giuseppe Peri  
Luca Longhi  
Tommaso Zoerle  
Mauro Tettamanti  
Cecilia Garlanda  
Anna Sigurtà  
Serenella Valaperta  
Alberto Mantovani  
Maria Grazia De Simoni  
Nino Stocchetti

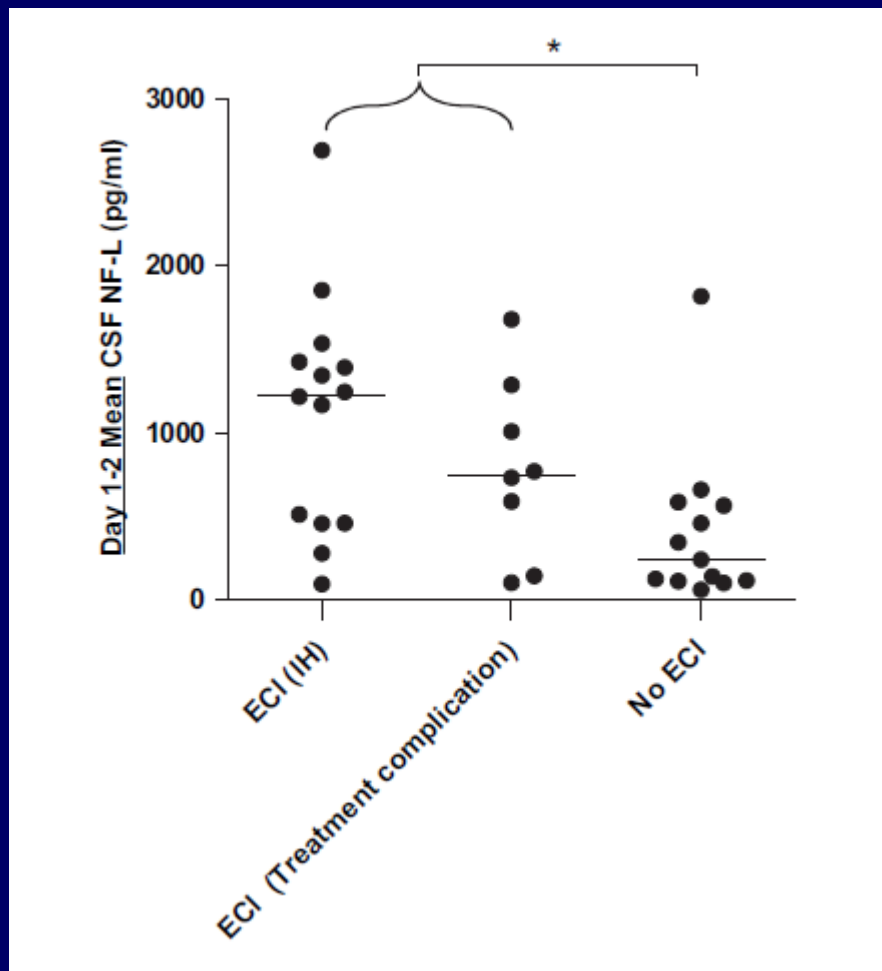
## **Cerebrospinal fluid pentraxin 3 early after subarachnoid hemorrhage is associated with vasospasm**





## Neurofilament light chain levels in ventricular cerebrospinal fluid after acute aneurysmal subarachnoid haemorrhage

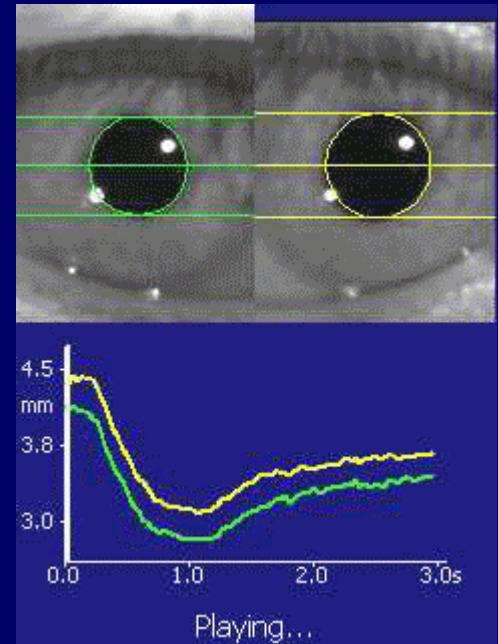
E R Zanier,<sup>1,2</sup> D Refai,<sup>3</sup> G J Zipfel,<sup>3</sup> T Zoerle,<sup>1</sup> L Longhi,<sup>1</sup> T J Esparza,<sup>4</sup> M L Spinner,<sup>4</sup>  
R J Bateman,<sup>4</sup> D L Brody,<sup>4</sup> N Stocchetti<sup>1</sup>



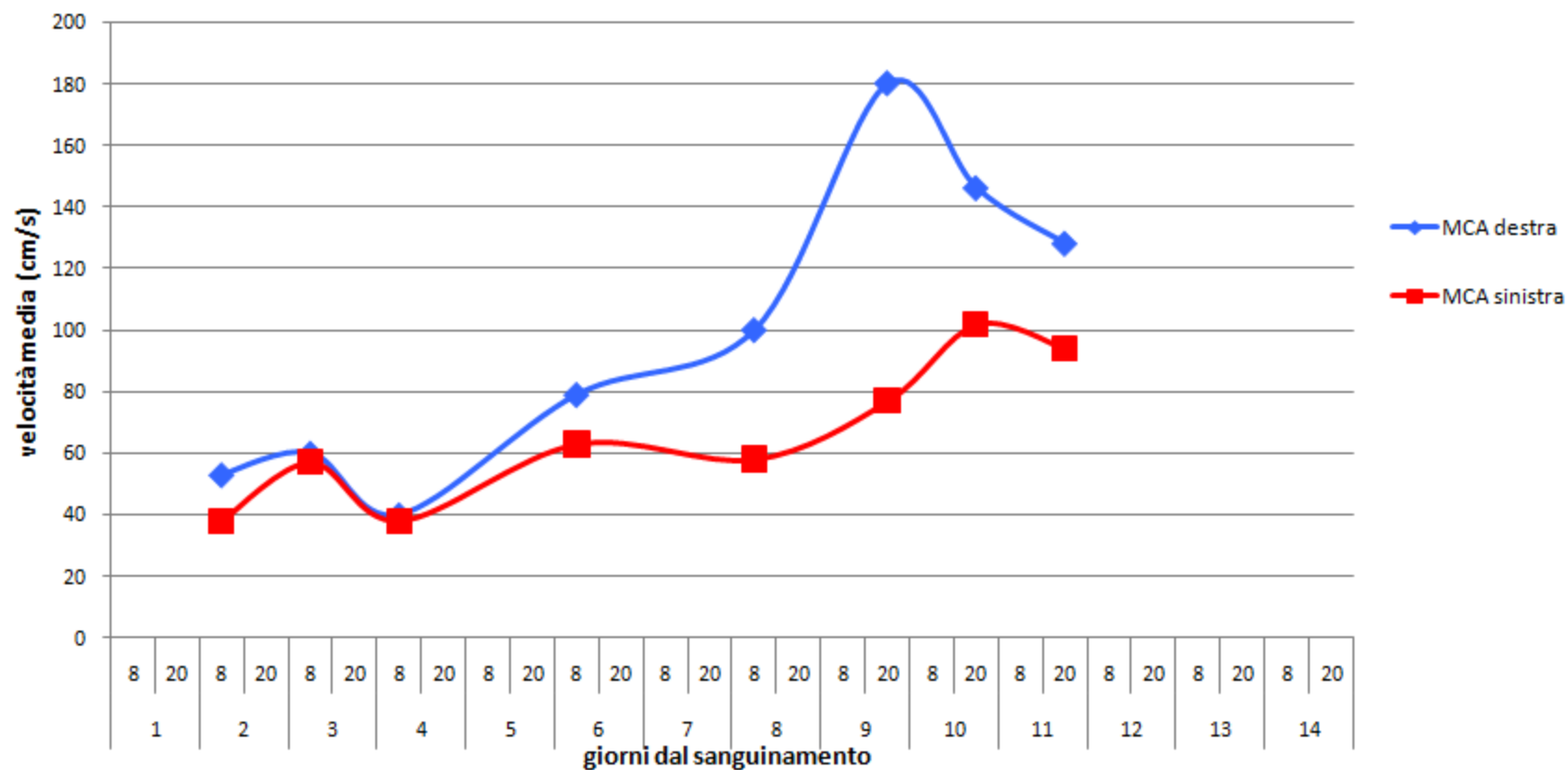


# Neurological observation











Narrowing



< Flow



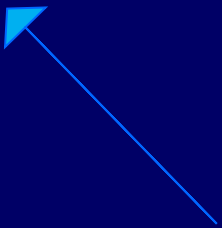
Inadequate delivery

Prevent VSP

Detect VSP

Reverse VSP

Preserve flow



0148-396X/82/1103-0337\$02.00/0

NEUROSURGERY

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## Clinical and laboratory reports

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# Treatment of Ischemic Deficits from Vasospasm with Intravascular Volume Expansion and Induced Arterial Hypertension

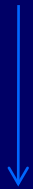
**Neal F. Kassell, M.D., Sydney J. Peerless, M.D., Quentin J. Durward, M.D., David W. Beck, M.D., Charles G. Drake, M.D., and Harold P. Adams, M.D.**

*Departments of Neurosurgery (N.F.K., D.W.B.) and Neurology (H.P.A.), University of Iowa Hospitals and Clinics, Iowa City, Iowa, and Departments of Neurosurgery (S.J.P., Q.J.D.) and Surgery (C.G.D.), University of Western Ontario, London, Ontario*



58 SAH patients  
with deficits

Start treatment



1 hour

47 complete or  
partial resolution



58 SAH patients  
with deficits

Start treatment



1 hour

47 complete or  
partial resolution




43 permanent resolution

4 transient resolution



... We commenced therapy by increasing the intravascular volume rapidly with blood and colloid solutions.

If this did not result in prompt improvement in the neurological impairments, we induced hypertension with vasopressor agents.




... We commenced therapy by increasing the intravascular volume rapidly with blood and colloid solutions.

If this did not result in prompt improvement in the neurological impairments, we induced hypertension with vasopressor agents.

The blood pressure was raised initially to a level estimated to exceed that required for reversal of the deficit ...

A 20 -100 torr increase in systolic arterial pressure was maintained for 12 hours to 8 days.

The maximal blood pressure limits were 240 systolic and 150 mean in patients whose aneurysms had been obliterated



# Triple-H

- Hemodilution  $\Rightarrow$  Ht 30 - 32
- Hypervolemia  $\Rightarrow$  PVC 10 - 12
- Hypertension  $\Rightarrow$   $\uparrow$  MAP 20 - 40 %

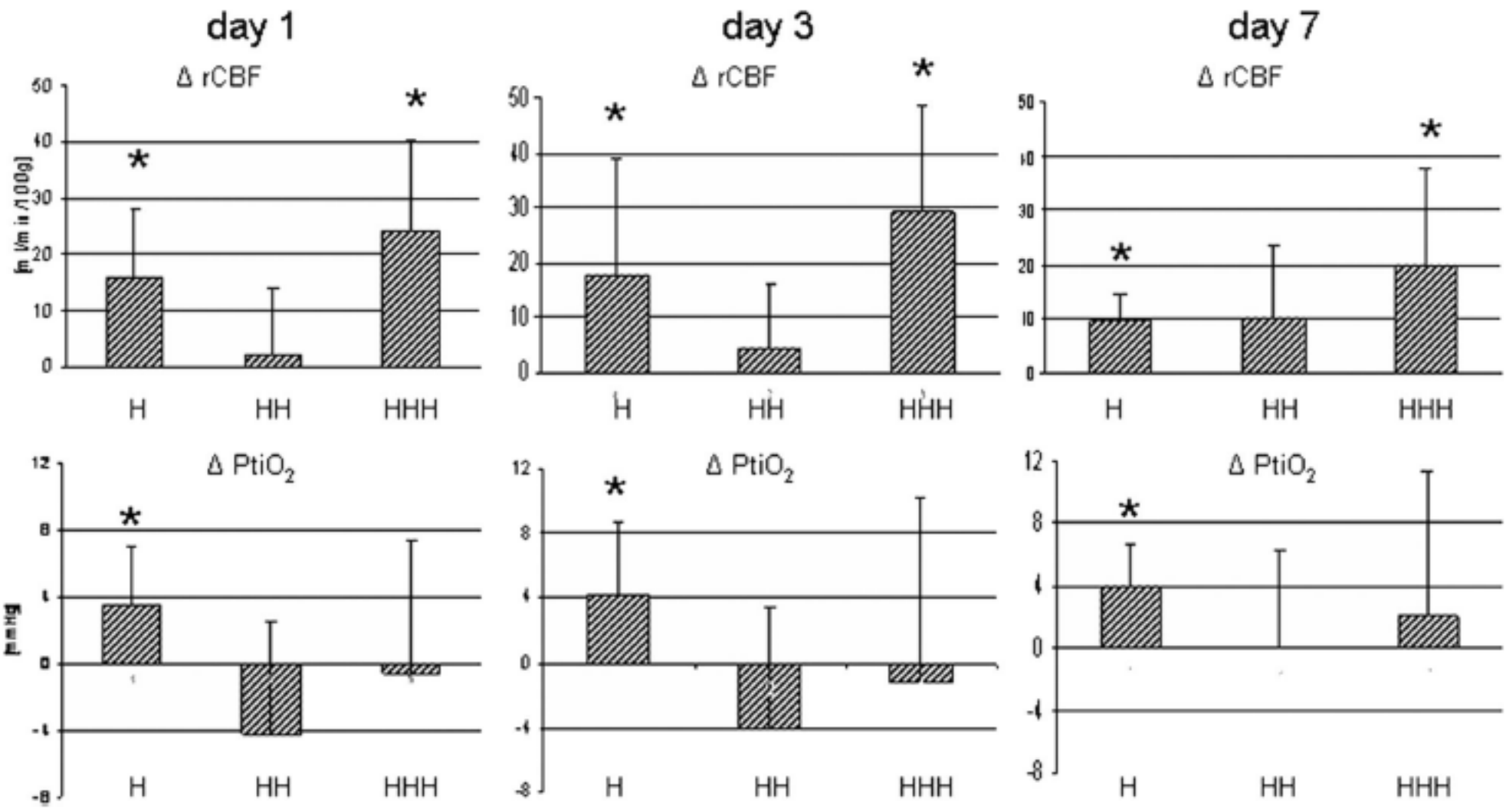




# Effects of hypervolemia and hypertension on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation after subarachnoid hemorrhage\*

Elke Muench, MD; Peter Horn, MD; Christian Bauhuf, MD; Harry Roth, MD; Mark Philipps, MD; Peter Hermann, DrScHum; Michael Quintel, MD, PhD; Peter Schmiedek, MD; Peter Vajkoczy, MD

n = 10





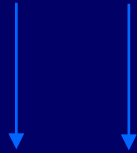
Narrowing



< Flow



microcirculation



Inadequate delivery

Prevent VSP

Detect VSP

Reverse VSP

Preserve flow

Reduce consumption



# SAH - Medical treatment of delayed cerebral ischemia

## Prevention of inadequate delivery

Hypovolemia

Hypothension

Low CPP

Hypoglycemia

Anemia

## Avoidance of increased demand

Fever

Seizures

