# Elucidation of Nitric Oxide (NO) Role in Vasospasm and Cortical Spreading Ischemia in a Primate Model of Aneurysmal Subarachnoid Hemorrhage

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Synthespreis der SGN 2008

SAH induced cerebral vasospasm occurs between day 4-9

20–30% experience delayed ischemic neurological deficits (DIND)

50% of these patients suffer severe permanent neurological dysfunction or death

# Delayed ischemic neurologicdeficits (DIND) after SAH vs angiography

- Cause of disability in 6.3% of SAH pts
- Cause of death in 7.2%
- Time course of DIND similar to angiographicaly visible vasospasm:
- However, angiographic vasospasm has only a positive predictive value for DIND of <50 %

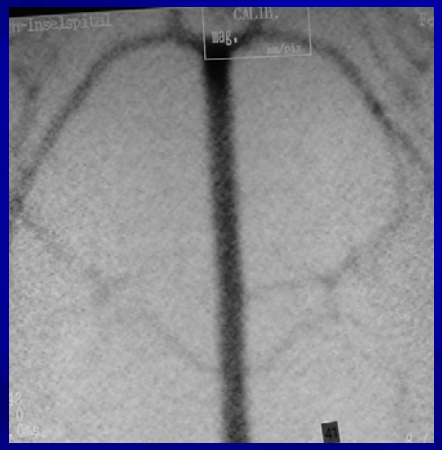
- Cerebral vasospasm ≠ delayed ischemic neurological deficit (DIND)

# Concepts of treatment

- Enhance Perfusion
- Reversal of Arterial Narrowing
- Prevention of Arterial Narrowing
- Ischemic Protection & Rescue

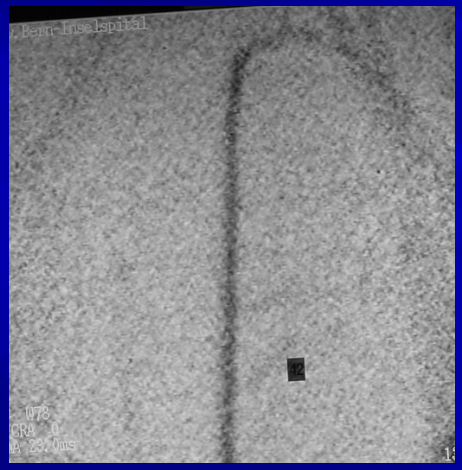
1. HHH Therapy
2. Enhance availability of nitric oxide (NO)

# Norepinephrine Induces Dilatation in the Rabbit Basilar Artery after Subarachnoid Hemorrhage In a Rabbit SAH model



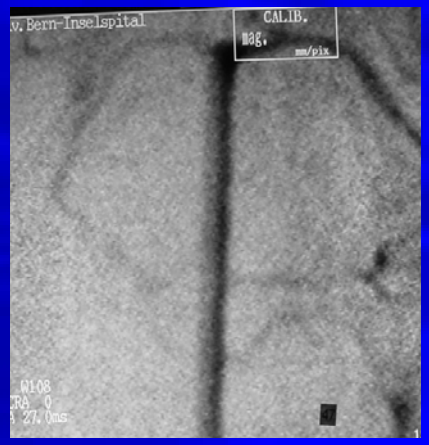
**Baseline angiogram on day 0 prior to SAH.**

**SBP = 81 mmHg**
**DBP = 57 mmHg**
**MAP = 65 mmHg**
**pCO2 = 53.6 mmHg**



**Follow-up angiogram on day 5 after SAH prior to initiation of NE infusion**

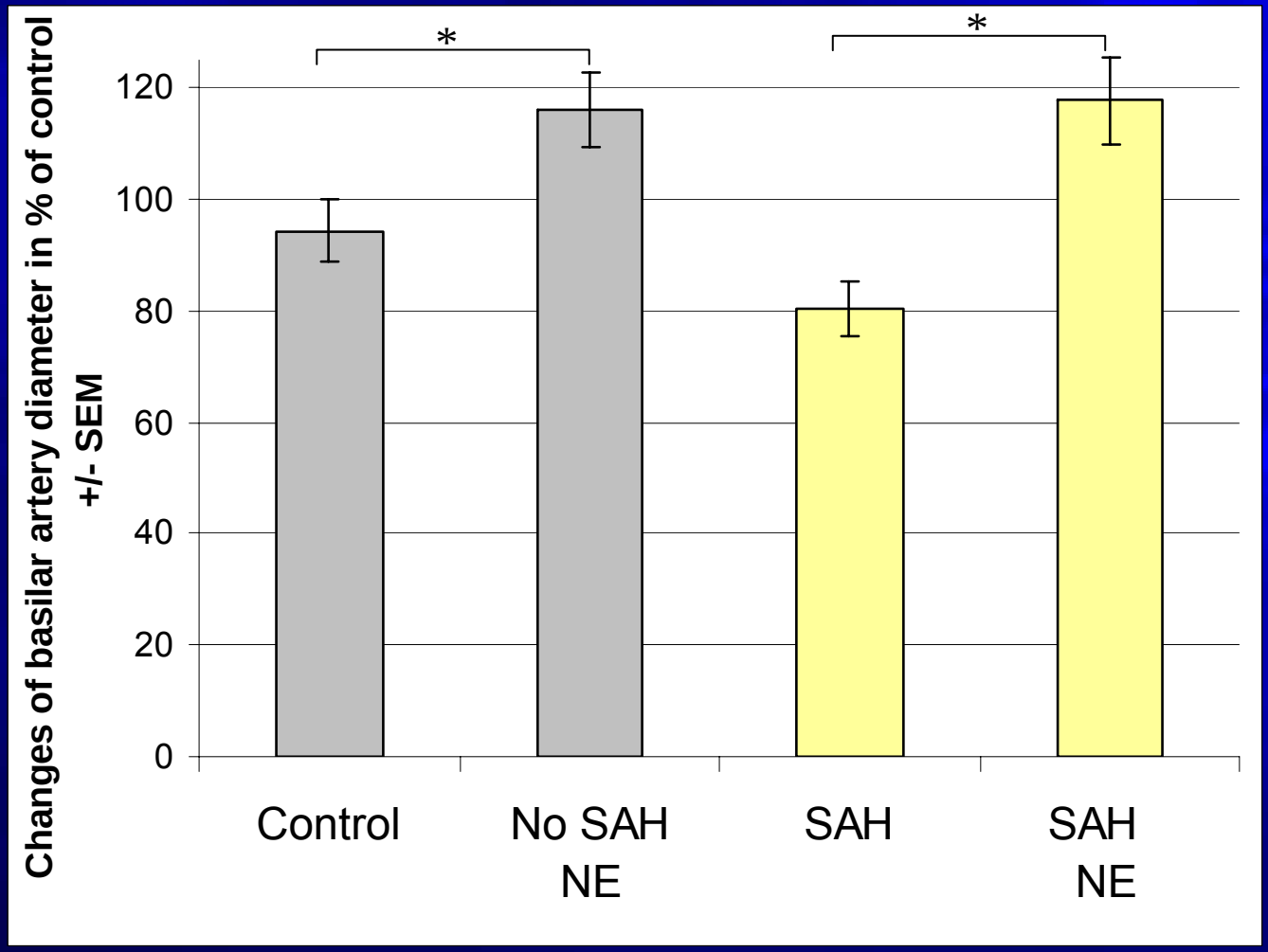
**SBP = 83 mmHg**
**DBP = 58 mmHg**
**MAP = 67 mmHg**
**pCO2 = 45.6 mmHg**
**(Width=57.3 % Baseline)**



**Follow up angiogram on day 5 after SAH during infusion of NE**

**SBP = 200 mmHg**
**DBP = 129 mmHg**
**MAP = 158 mmHg**
**pCO2 = 45.6 mmHg**
**(Width=160 % Baseline)**

# Changes of Basilar Artery Diameter




*p < 0.05

# Enhanced availability of nitric oxide (NO)

- Decreased availability of nitric oxide (NO) in the arterial walls of the circle of Willis has been linked to development of delayed cerebral vasospasm after aneurysmal subarachnoid hemorrhage (aSAH) in both clinical and experimental settings *(PlutaRM, Neurol Res 2006 Oct;28:730-737 )*

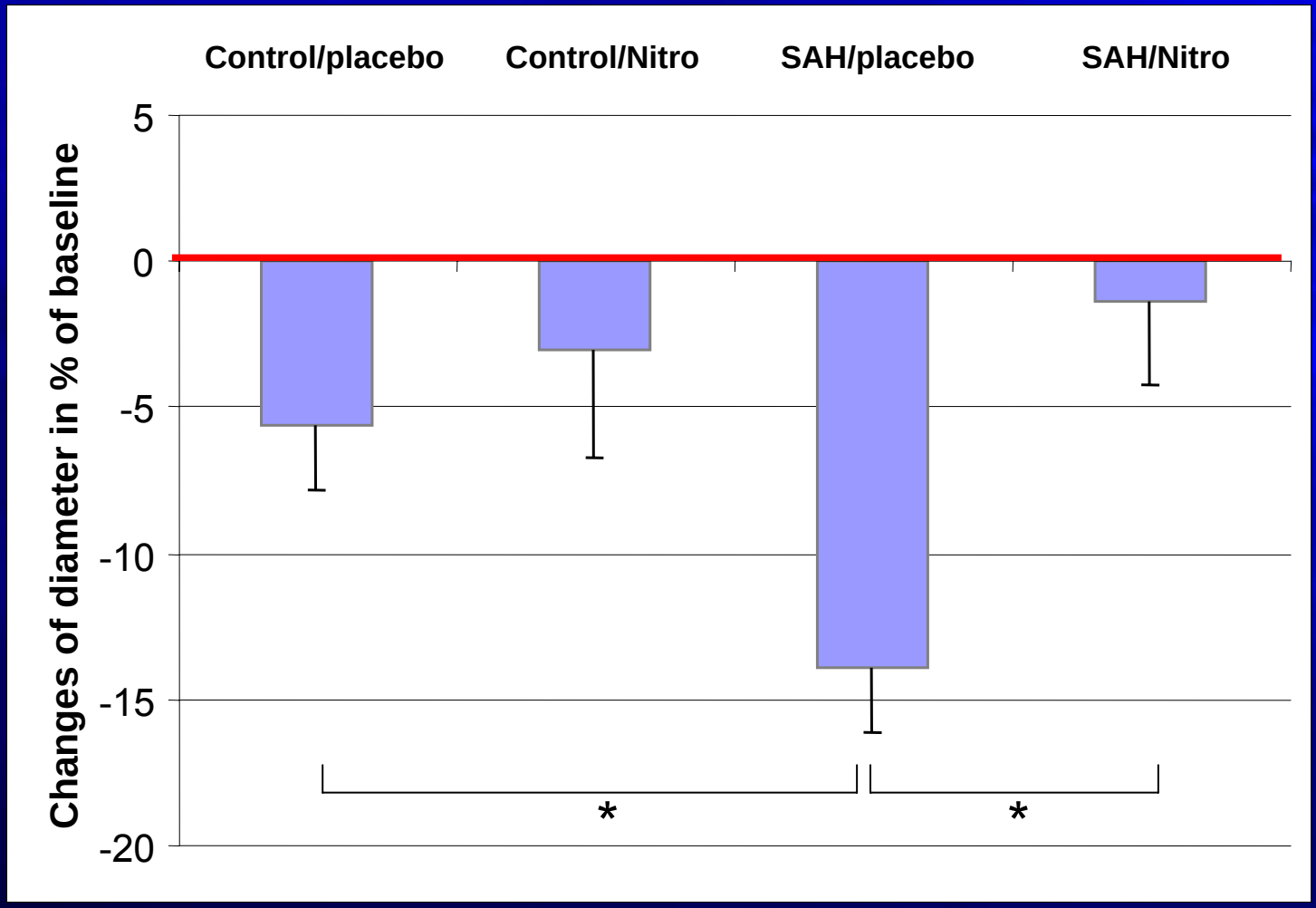
- Main problem: local delivery of high concentrations of NO or NO donors

- Recently, it was reported that sodium nitrite is a stable reservoir of NO and when given intravenously, can prevent arteriographic vasospasm in a primate model of aSAH


- Cosby K, Partovi KS, Crawford JH, et al. Nat Med 2003 Dec;9:1498-1505.
- Pluta RM, Dejam A, Grimes G, Gladwin MT, Oldfield EH. JAMA 2005 Mar 23;293:1477-1484.

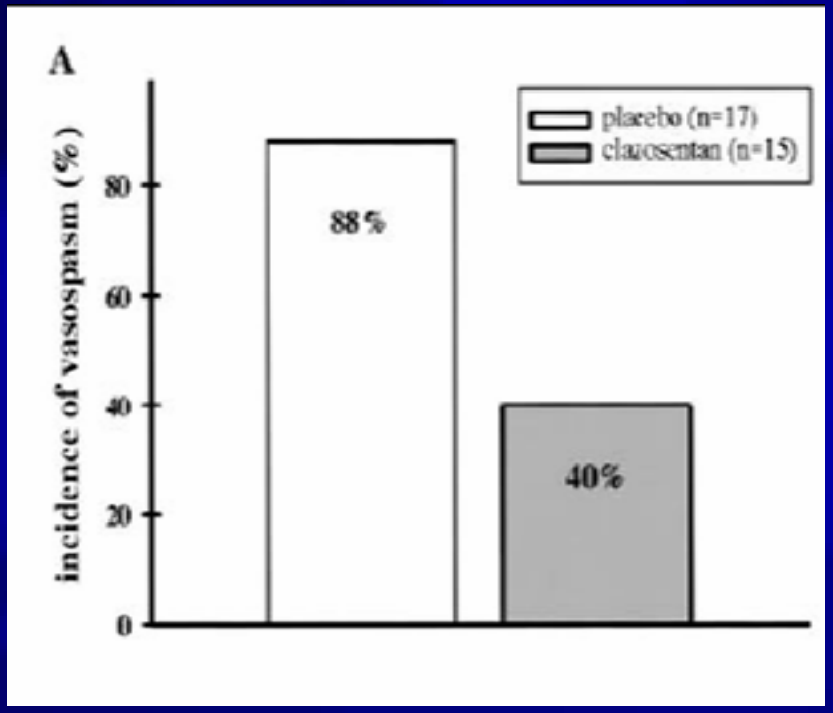

- Additionally we could demonstrate that intrathecal continuous administration of nitroglycerin as a NO donor prevents CVS in a rabbit SAH model

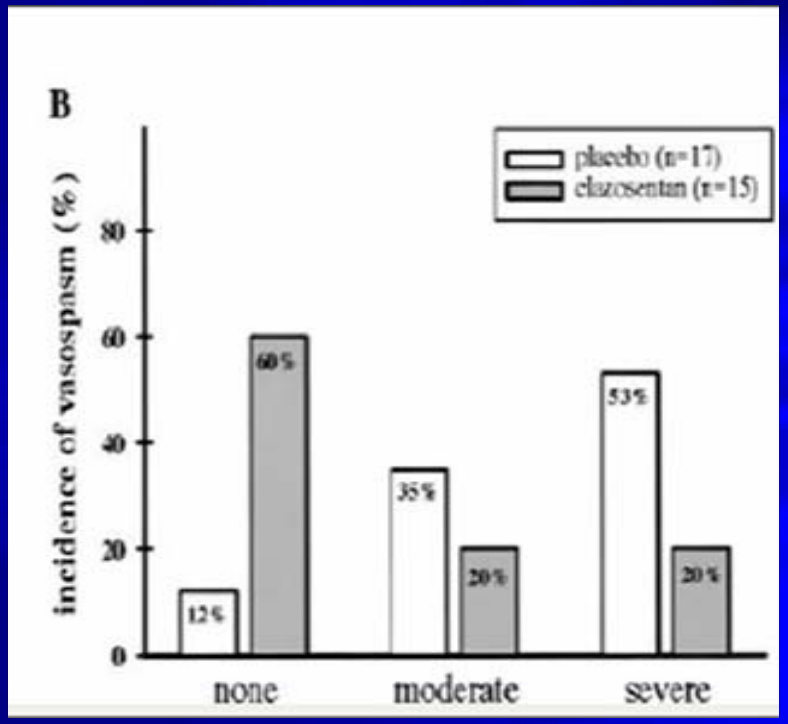
- Prophylactic continuous intrathecal administration of nitroglycerine prevents vasospasm of the basilar artery in the rabbit SAH model
- No toxic effects could be demonstrated in this study




* P < 0.05

# The Clazosentan study




- + Clazosentan reduces incidence of angiographic vasospasm
- - No improvement in clinical outcome at 3 months (DIND, mortality)

Macdonald, Pluta et al, Nature Clinical Pract Neurol, 2007

Vajkoczy, Meyer et al, Abstract, Internat. Meeting on Cerebral Vasospasm 2006

# COSBID

- The Co-Operative Study on Brain Injury Depolarizations (COSBID)
- a prospective clinical multicenter study
- demonstrated delayed clusters of cortical spreading depolarization (CSD) in SAH patients
- In many patients, clusters of prolonged depolarization occurred
- These patients developed ischemic infarcts in the recording area, indicating that CSDs may be linked to DINDs

Dreier JP, Woitzik J, Fabricius M, et al. *Brain* 2006 Dec;129:3224-3237.

# New Concept

- delayed cerebral vasospasm is not the only factor responsible for poor outcome after successful treatment of aSAH

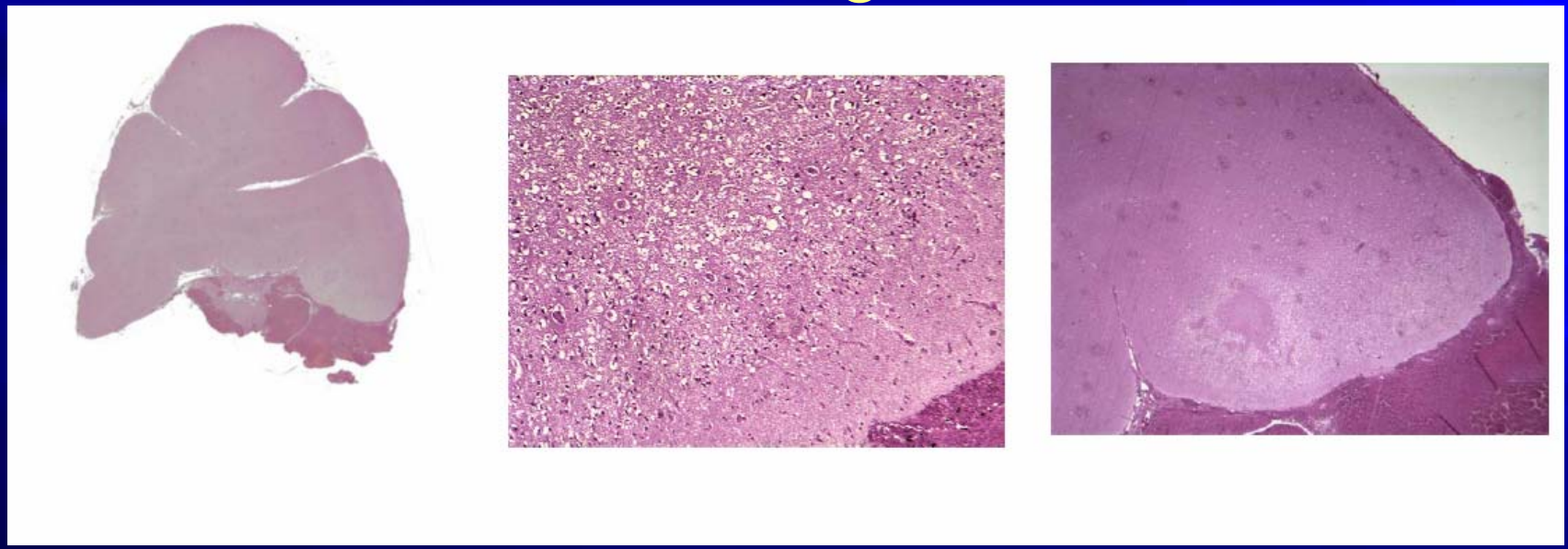
- rather, there are two important factors responsible for the clinical outcome:

  (1) delayed spasm of large cerebral arteries

  (2) spreading depolarizations producing cortical infarcts

# Primate model for cortical ischemia

- **Day 14 post SAH**
- - cortical laminar necrosis
- - no territorial infarct
- - no white matter changes



- Schatlo et al, *abstract award: AANS 2008*

# Cortical Spreading Depression


1. Depolarization
2. Neuronal metabolic suppression
3. Disturbance of neuronal microenvironment, K+↑
4. Need of ATPase to pump K+ back into cell
5. Increased metabolic demand
6. Reactive hyperaemia with increased demand of Nitric Oxide

Petzold GC, Haack S, von Bohlen Und HO, et al. *Stroke* 2008 Apr;39:1292-1299.

# Goals

- we will employ a primate model of aSAH that has been used in the Vascular Laboratory of the Surgical Neurology Branch, NINDS for several years to study delayed cerebral vasospasm

  Pluta RM, Dejam A, Grimes G, Gladwin MT, Oldfield EH. *JAMA* 2005 Mar 23;293:1477-1484

- our hypothesis is that oral administration of sodium nitrite, especially in the presence of ascorbic acid will prevent development of delayed cerebral vasospasm and cortical infarcts by preventing cortical spreading ischemia

  Kytzia A, Korth HG, Sustmann R, de GH, Kirsch M. *Chemistry* 2006 Nov 24;12:8786-8797

- **to establish the most effective oral sodium nitrite and/or sodium nitrite/ascorbic acid dose that does not cause a hypotensive response or other side effects (methemoglobinemia) but which prevents vasospasm and/or cortical infarcts**

- ***the ultimate goal:*** **is to prove that a primate model of aSAH is adequate to examine the therapeutic effect of drugs which affect development of delayed cerebral vasospasm and delayed ischemic neurological deficits**

# Thank You

## AND

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