Vasospasm after Subarachnoid Hemorrhage: Current Standard Therapies and Future Directions

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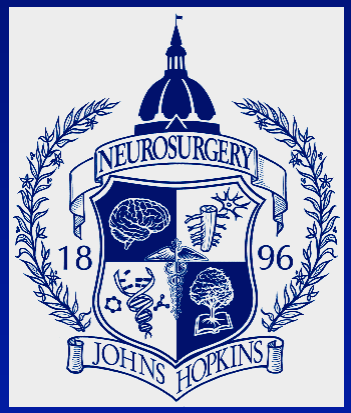

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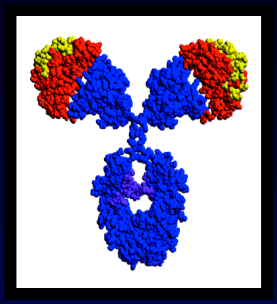
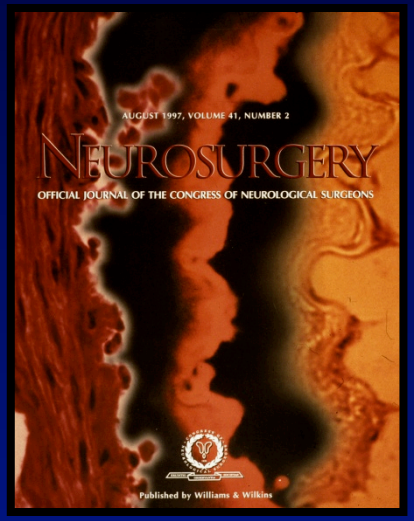
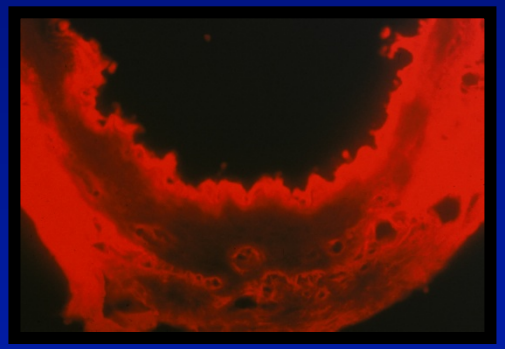
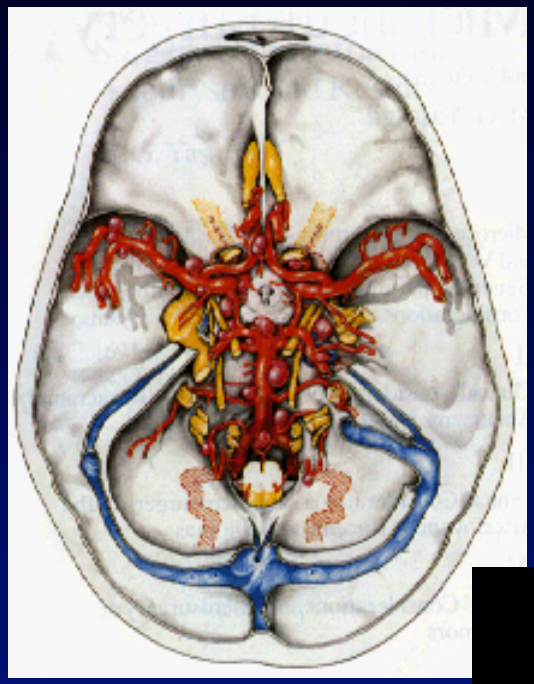
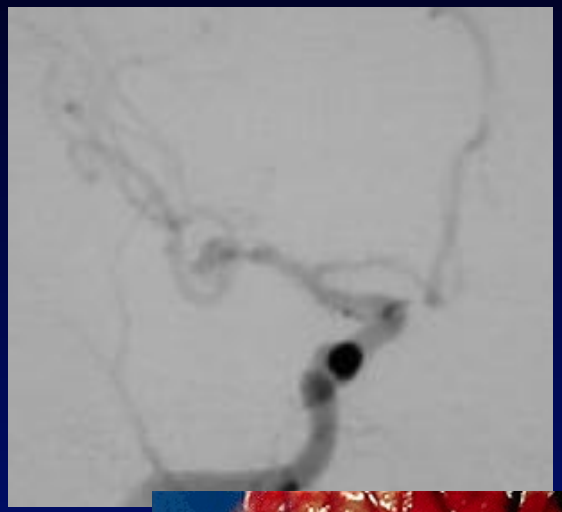


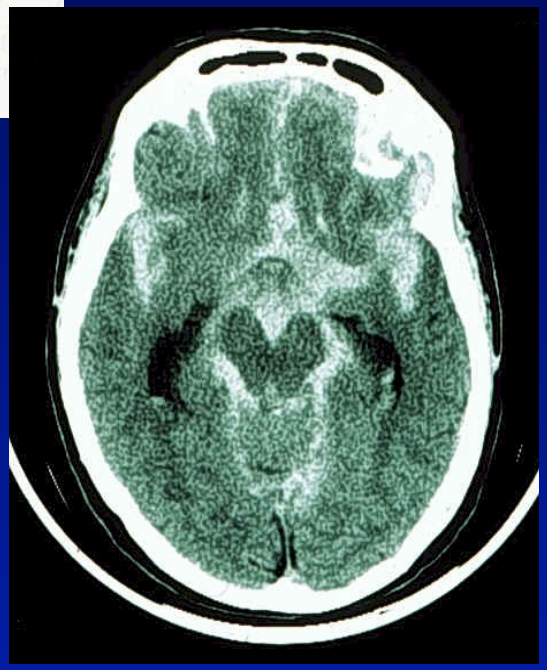


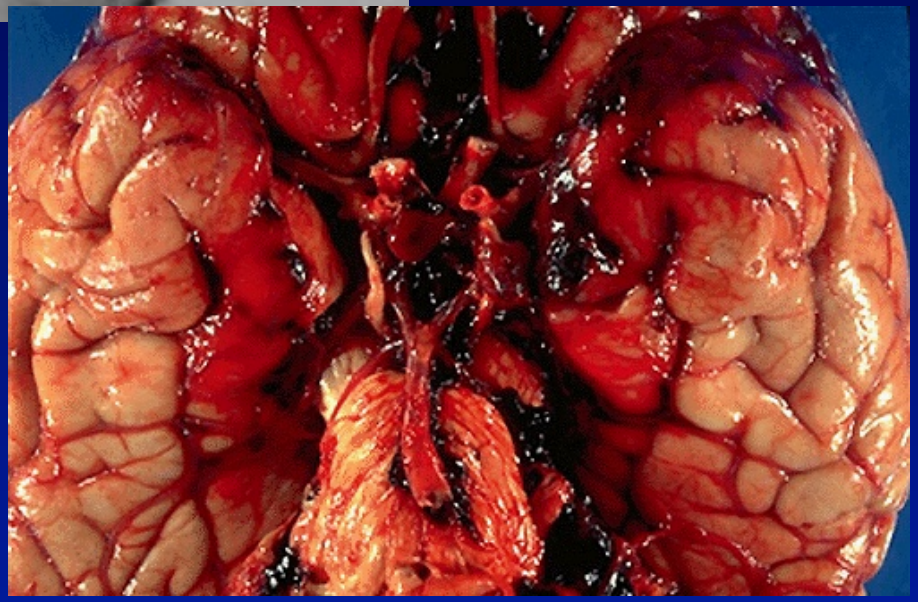


Aneurysmal Subarachnoid Hemorrhage



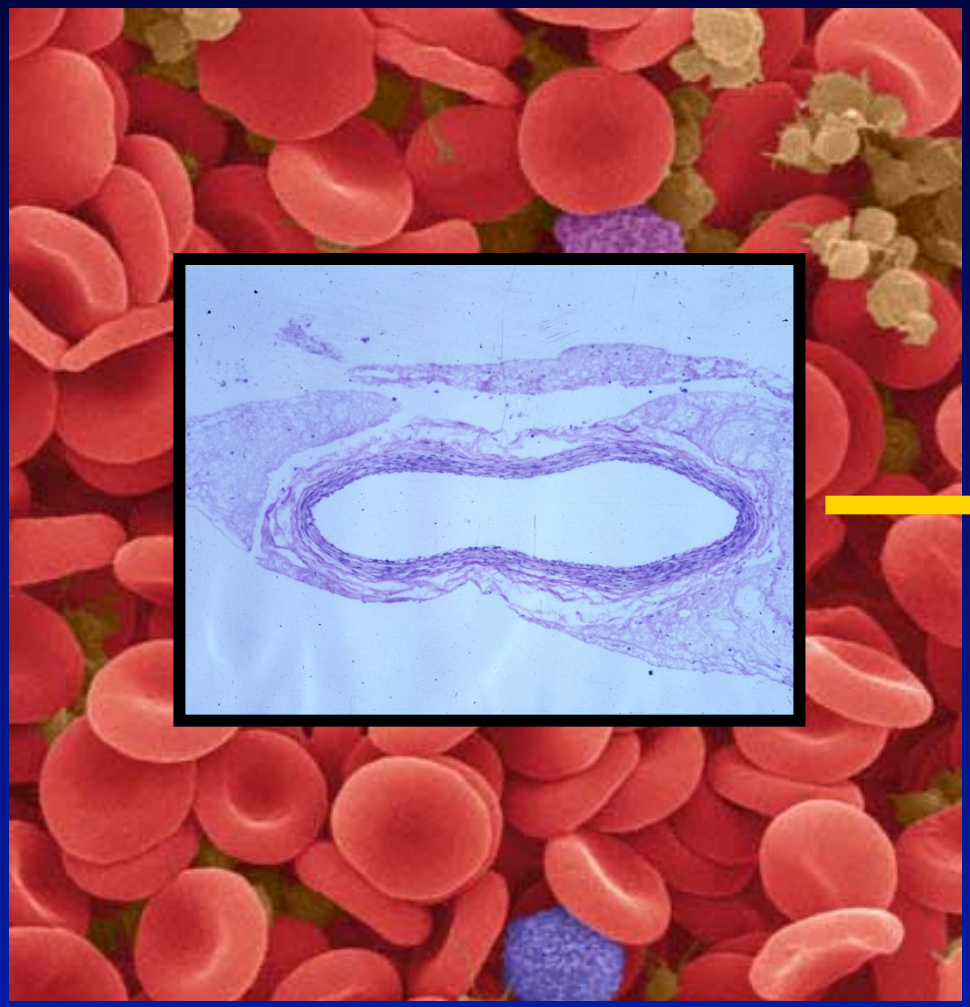


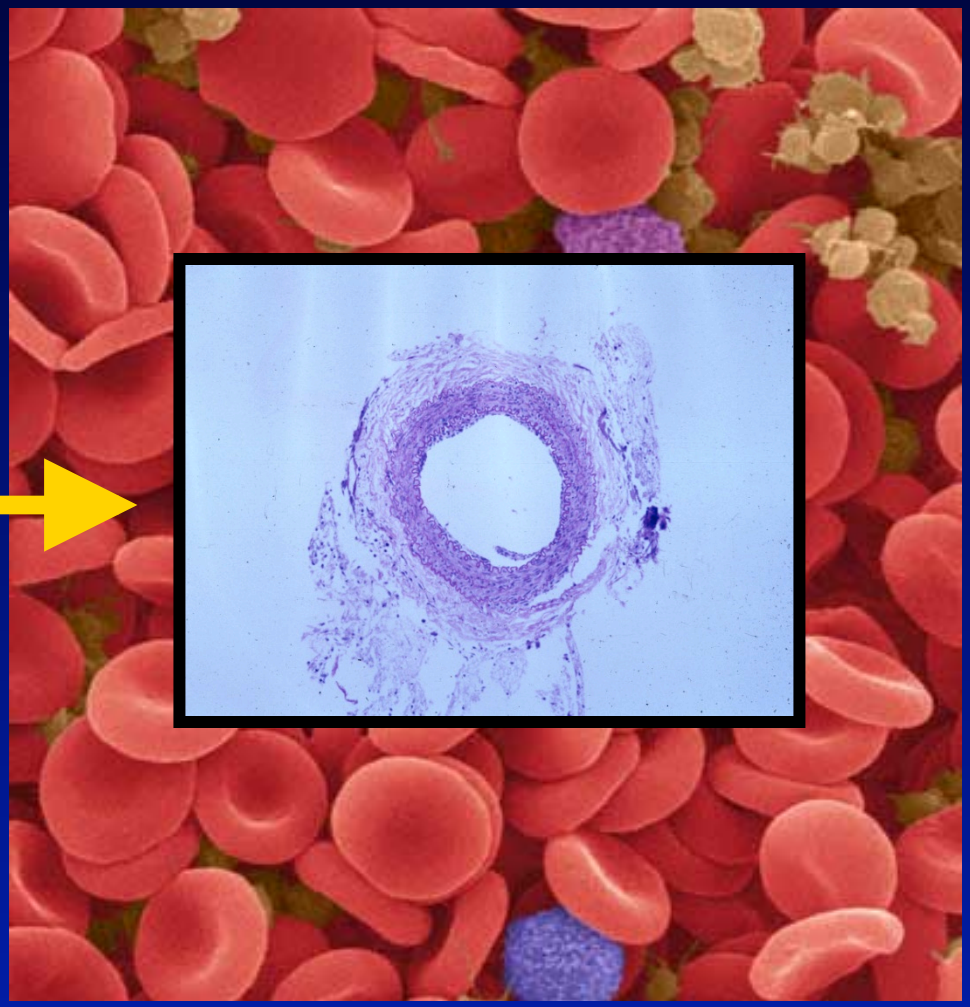




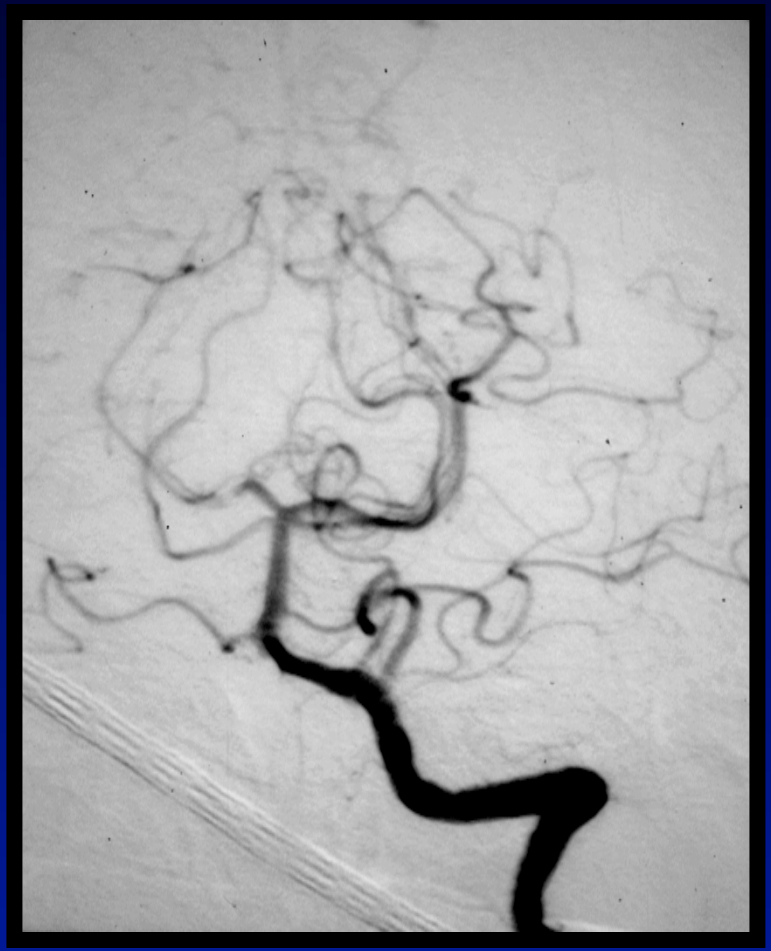
Chronic Post-Hemorrhagic Vasospasm (VSP)

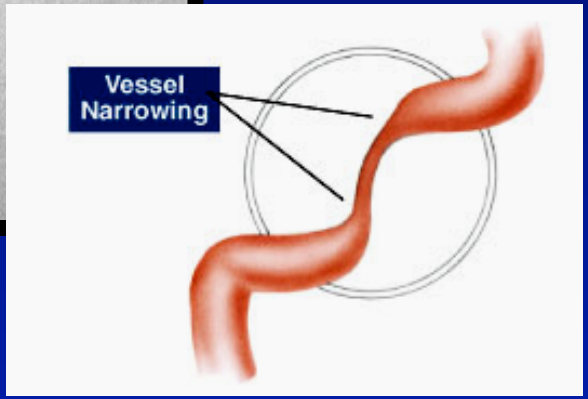
In humans, VSP develops 4 to 21 days after SAH, peaks at 7-10 days



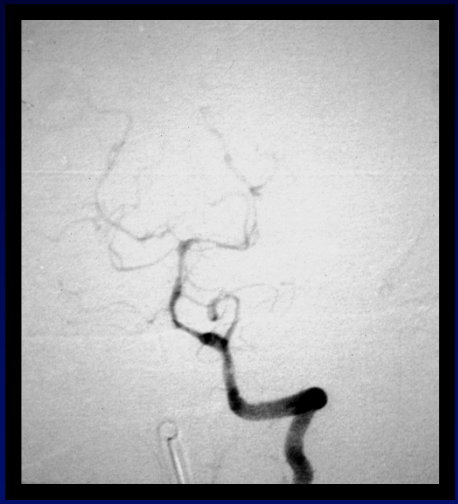


Case Study: Angiographic vasospasm 6 days after SAH





Earliest Descriptions of Vasospasm after SAH



E. Graeme Robertson
(Melbourne, Australia)
"Cerebral lesions due to intracranial aneurysms."
Brain 72: 150, 1949

Arthur Ecker and Paul A. Riemenschneider
(Syracuse, New York)
"Arteriographic demonstration of spasm of the intracranial arteries with special reference to saccular arterial aneurysms."
Journal of Neurosurgery 8: 660, 1951

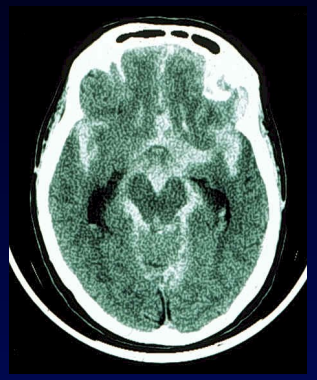
Current Standard Therapies

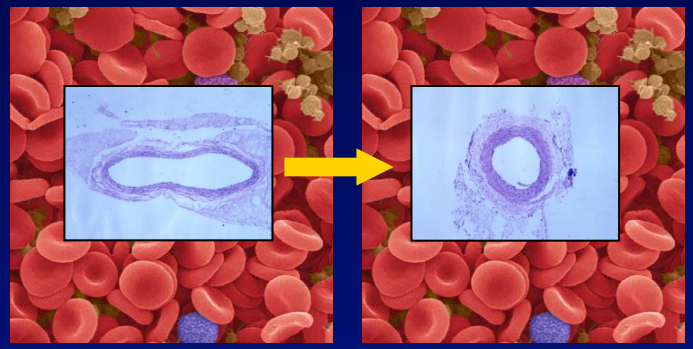
1. "Triple H" Therapy
   - Hypertonic saline solutions
   - IABP counterpulsation

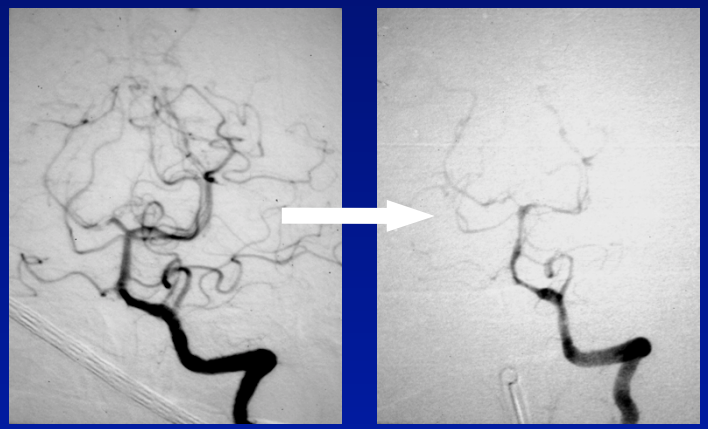
2. Calcium channel blockers
   - Nimodipine
   - Nicardipine?

3. Angioplasty

4. Statins



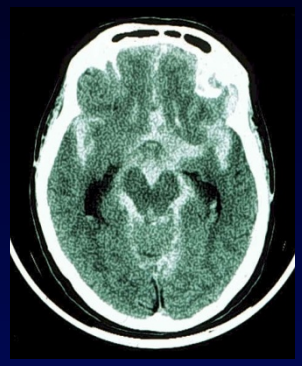




Hypertensive, Hypervolemic, Hemodilutional ("Triple H") Therapy evolved from 1972-1982

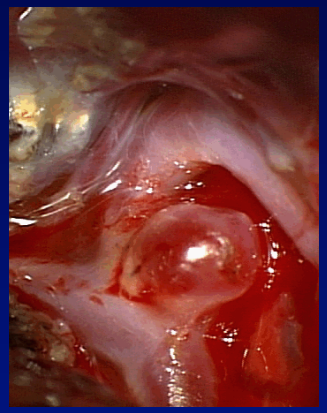
Hypertensive therapy:

"The treatment of brain ischemia with vasopressor drugs"
G. Wise et al. *Stroke* 3: 135, 1972
(Ohio State University Hospitals, Columbus, Ohio)



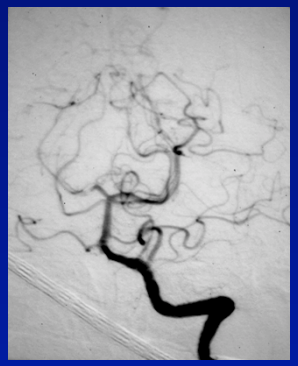
Hypervolemic therapy:

"Timing and perioperative care in intracranial aneurysm surgery"
W. E. Hunt and E. J. Kosnick *Clin Neurosurg* 21: 79, 1972
[7 patients with vasospasm treated with colloid solutions and phenylephrine]



Hemodilutional therapy:

"Observations during hypervolemic hemodilution of patients with acute focal cerebral ischemia"
J. H. Wood and A. S. Fleischer *JAMA* 248: 2999, 1982
[9 patients treated with albumin or dextran to mean Hct 32%]



Hypertensive, Hypervolemic, Hemodilutional therapy:

"Treatment of ischemic deficits from vasospasm with intravascular volume expansion and induced arterial hypertension"
N. Kassell and C.G. Drake et al. *Neurosurgery* 11: 337, 1982
(University of Iowa Hospitals, Iowa City, Iowa, and University of Western Ontario, London, Ontario)

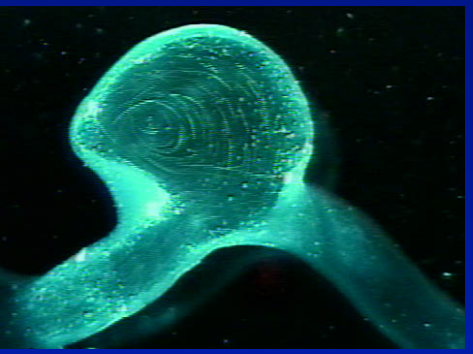
Hypertensive, Hypervolemic, Hemodilutional ("Triple H") Therapy

1. **Hypervolemia:**
   - Upon admission, IVF started at 100 – 200 cc/hr
   - If vasospasm develops:
     - IVF increased to maximize cardiac performance
     - **GOAL**:
       - PAWP 14-16 mm Hg
       - Swan-Ganz catheter inserted (PiCCO catheters?)
       - CVP is an unreliable index of cardiac performance

"Cardiac performance indices during hypervolemic therapy for cerebral vasospasm"
M. L. Levy and S. L. Giannotta Jl Neurosurgery 75: 27, 1991
(University of Southern California, Los Angeles, California)

Hypervolemic, Hypertensive, Hemodilutional ("Triple H") Therapy

2. **Hypertension:**
   - Upon admission, all anti-hypertensives drugs discontinued
   - If vasospasm develops:
     - BP increased to maximize cardiac performance
     - **GOAL**:
       - BP raised 25% above baseline
         (Systolic BP > 180 mm Hg or MAP > 120 mm Hg)
       - BP is titrated until deficit is reversed
     - Norepinephrine *(Levophed)* or Phenylephrine *(Neosynephrine)*



"Triple-H therapy in the management of aneurysmal subarachnoid hemorrhage"
J. Sen et al. *The Lancet Neurology* 2: 614, 2003
(National Hospital, Queen Square, London, UK)

Relative Importance of Hypertension vs. Hypervolemia

	Increase in brain PO_2	Complications
Hypervolemia	12%	53%
Moderate hypertension	90%	8%
Aggressive hypervolemic hypertension	60%	50%

"Relative importance of hypertension compared with hypervolemia for increasing cerebral oxygenation in patients with cerebral vasospasm after subarachnoid hemorrhage"

A. Raabe et al. *Jl Neurosurg* 103: 974, 2005

(Goethe University, Frankfurt am Main, and University of Leipzig, Germany)

Hypervolemic, Hypertensive, Hemodilutional ("Triple H") Therapy

3. **Hemodilution:**
   - Optimal rheological performance and oxygenation is obtained with a hematocrit of 30-35 (Hgb 10-12)

"Experimental hypervolemic hemodilution: physiological correlations of cortical blood flow, cardiac output, and intracranial pressure with fresh blood viscosity and plasma volume"
J. H. Wood et al. *Neurosurgery* 14: 709, 1984
[Physiological experiments in 7 dogs]

"Rheology of the cerebral circulation"
D. B. Kee and J. H. Wood et al. *Neurosurgery* 15: 125-131, 1984
[Review article]

Fine-Tuning "Triple H" Therapy

1. **Hypertonic saline solutions**
   - Ideal for hypervolemic therapy
   - Corrects sodium deficits in CSW
   - Reduces cerebral edema

2. **Intra-Aortic Balloon Pump Counterpulsation**
   - Salvage procedure during triple H therapy
   - Stunned myocardium, CHF, sepsis

"Intra-aortic balloon pump counterpulsation in the management of concomitant Cerebral vasospasm and cardiac failure after subarachnoid hemorrhage"
P. J. Apostolides et al. *Neurosurgery* 38: 1056, 1996
(Barrow Neurological Institute, Phoenix, Arizona)

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Vol. 11, No. 3, pp. 178–184
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Administration of Hypertonic (3%) Sodium Chloride/Acetate in Hyponatremic Patients with Symptomatic Vasospasm Following Subarachnoid Hemorrhage

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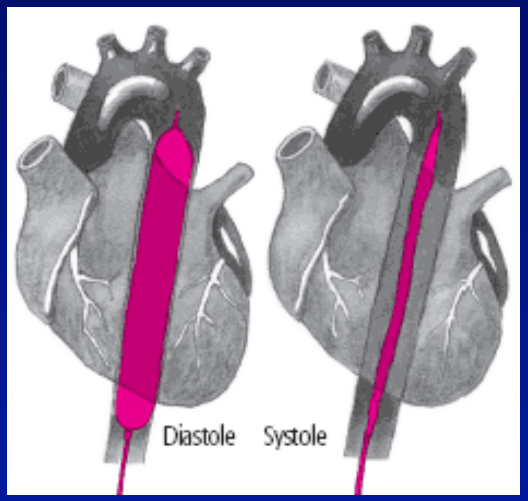
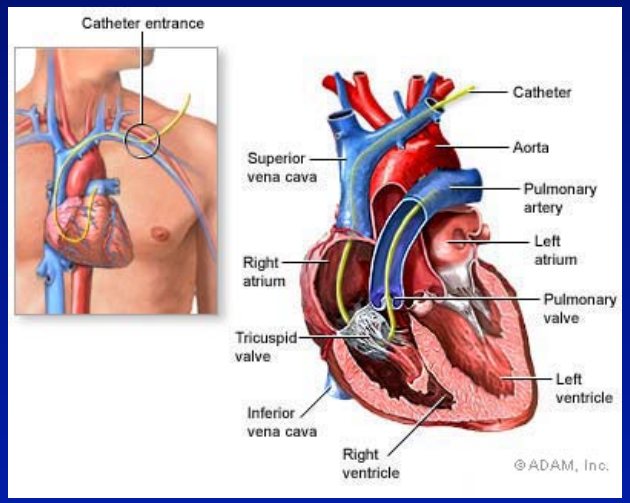
Summary: A retrospective study was carried out to evaluatez the effect of hypertonic (3%) saline chloride/acetate on various hemodynamic parameters in mildly hyponatremic patients with symptomatic vasospasm following aneurysmal subarachnoid hemorrhage (SAH). We identified 29 hyponatremic (serum sodium < 135 mEq/L) patients who received hypertonic (3%) sodium chloride/acetate as a continuous infusion. Administration of hypertonic (3%) sodium chloride/acetate resulted in higher central venous pressures and positive fluid balance, with a concomitant increase in serum sodium and chloride concentrations without metabolic acidosis. There were no changes in mean cerebral blood flow velocities after infusion of hypertonic (3%) sodium chloride/acetate. We found no reports of congestive heart failure, pulmonary edema, metabolic acidosis, coagulopathy, intracranial hemorrhages, or central pontine myelinolysis in any of these patients. We conclude that hypertonic (3%) sodium chloride/acetate can be administered to patients with mild hyponatremia in the setting of symptomatic vasospasm following SAH without untoward effects. Sample size and limitations of a retrospective analysis preclude conclusions about safety and efficacy of hypertonic (3%) sodium chloride/acetate administration in this patient population. However, our results support justification for a prospective, randomized, double-blind trial of hypertonic (3%) sodium chloride/acetate versus normal saline in patients with symptomatic vasospasm following SAH. **Key Words**: Saline—Hypertonic—Vasospasm—Cerebral—Subarachnoid.



Complications of "Triple H" Therapy

Pulmonary edema	17%
Sepsis	13%
Dilutional hyponatremia	3%
Subclavian vein thrombosis	3%
Myocardial infarction	2%
Pneumothorax	1%



"Triple-H therapy in the management of aneurysmal subarachnoid hemorrhage"
J. Sen et al. *The Lancet Neurology* 2: 614, 2003
(National Hospital, Queen Square, London, UK)

Calcium channel blockers in vasospasm

CEREBRAL ARTERIAL SPASM — A CONTROLLED TRIAL OF NIMODIPINE IN PATIENTS WITH SUBARACHNOID HEMORRHAGE

George S. Allen, M.D., Ph.D., Hyo S. Ahn, M.D., Thomas J. Preziosi, M.D., Roy Battye, M.B., Ch.B., Stephen C. Boone, M.D., Ph.D., Shelley N. Chou, M.D., Ph.D., David L. Kelly, M.D., Bryce K. Weir, M.D., Ruth A. Crabbe, R.N., M.S.N., Paula J. Lavik, R.N., Shelley B. Rosenbloom, M.D., Frank C. Dorsey, Ph.D., Charles R. Ingram, Ph.D., David E. Mellits, Sc.D., Linda A. Bertsch, R.N., Donald P. J. Boisvert, M.D., Mary B. Hundley, R.N., M.S., Rayetta K. Johnson, R.N., Jo A. Strom, R.N., and Carole R. Transou, R.N.

Abstract We enrolled 125 neurologically normal patients with intracranial aneurysms in a multi-institution, prospective, double-blind, randomized, placebo-controlled trial within 96 hours of their subarachnoid hemorrhage, to determine whether treatment with the calcium blocker nimodipine would prevent or reduce the severity of ischemic neurologic deficits from arterial spasm. A deficit from cerebral arterial spasm that persisted and was severe or caused death by the end of the 21-day treatment period occurred in 8 of 60 patients given placebo and in 1 of 56 given nimodipine (P = 0.03, Fisher's exact test). Analysis of the amount of basal subarachnoid blood on pre-entry CAT scans in patients with deficits from spasm showed that an increase in subarachnoid blood was not associated with a worse neurologic outcome among patients who received nimodipine, unlike the situation in patients given a placebo. There were no side effects from nimodipine. We conclude that nimodipine should be given to patients who are neurologically normal after subarachnoid hemorrhage in order to reduce the occurrence of severe neurologic deficits due to cerebral arterial spasm. (N Engl J Med. 1983; 308:619-24.)

1. <u>Nimodipine</u>
   - Introduced in 1983 at Johns Hopkins
   - Improves neurological outcomes
   - Does not prevent vasospasm
   - May induce hypotension
   - We stop it at 14 days

"Efficacy of prophylactic nimodipine for delayed ischemic deficit after subarachnoid hemorrhage: a meta-analysis"
F. G. Barker and C. Ogilvy *<u>Jl Neurosurg</u>* 84: 405, 1996

2. <u>What about nicardipine?</u>
   - Can be given IV
   - Reduces incidence of symptomatic vasospasm but does not improve outcomes at 3 months as compared to standard therapy

"A randomized controlled trial of high-dose intravenous nicardipine in aneurysmal subarachnoid hemorrhage. A report of the Cooperative Study."
E. C. Haley, N. F. Kassell, J. C. Torner *<u>Jl Neurosurg</u>* 78: 537, 1993
(University of Virginia, Charlottesville, Virginia)

Angioplasty in Vasospasm

- Introduced in 1984
- We consider it standard therapy
- If we do not see improvement within 6-12 hours after starting triple H therapy, we proceed immediately to angiography and angioplasty

"Balloon catheter technique for dilatation of constricted cerebral arteries after aneurysmal SAH"
Y. N. Zubkov et al. *Acta Neurochir (Wien)* 70: 65, 1984
[Initial report 33 patients]

"Endovascular treatment of cerebral vasospasm: transluminal balloon angioplasty, intra-arterial papaverine, intra-arterial nicardipine"
B. L. Hoh and C. S. Ogilvy *Nus Clin N Am* 16: 501, 2005
[Review article]

HMG CoA reductase inhibitors (statins):

Inhibit ICAM-1 expression
and
Upregulate eNOS (increase NO production)

Seeger H, Wallwiener D, Mueck AO
Lipid-independent effects of an estrogen-statin combination: Inhibition of expression of adhesion molecules and plasminogen activator inhibitor I in human endothelial cell cultures
Climacteric 4: 209-214, 2001

Laufs U, La Fata V, Plutzky J, Liao JK
Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors
Circulation 97: 1129-1135, 1998

Effects of Acute Treatment With Pravastatin on Cerebral Vasospasm, Autoregulation, and Delayed Ischemic Deficits After Aneurysmal Subarachnoid Hemorrhage

TABLE 3. Results of the Primary End Points Vasospasm and Impaired Autoregulation

Incidence of Vasospasm	Total (%)	Placebo (%)	Statin (%)	*P**
Vasospasm	42 (52.5)	25 (62.5)	17 (42.5)	0.006
Severe vasospasm	19 (23.5)	12 (30.0)	7 (17.5)	0.044
Duration of Vasospasm, days	Total (95% CI)	Placebo (95% CI)	Statin (95% CI)	*P*†
Vasospasm	2.7 (1.9 to 3.5)	3.0 (1.8 to 4.2)	2.3 (1.2 to 3.4)	0.398
Severe vasospasm	0.8 (0.4 to 1.2)	1.2 (0.5 to 1.9)	0.5 (0.1 to 0.8)	0.068
Impaired Autoregulation, days	Total (95% CI)	Placebo (95% CI)	Statin (95% CI)	*P*†
Ipsilateral	4.2 (3.2 to 5.1)	5.3 (3.9 to 6.8)	3.0 (1.9 to 4.1)	0.011
Contralateral	2.7 (1.9 to 3.5)	3.7 (2.3 to 5.1)	1.6 (0.9 to 2.3)	0.008

**P* for the log-rank test; †*P* for the *t* test

Conclusion—Acute treatment with pravastatin after aSAH is safe and ameliorates cerebral vasospasm, improves cerebral autoregulation, and reduces vasospasm-related DID. Unfavorable outcome at discharge was reduced primarily because of a reduction in overall mortality. This is the first demonstration of clinical benefits with immediate statin therapy for an acute cerebrovascular disorder. (***Stroke*. 2005;36:1627-1632.)

Simvastatin Reduces Vasospasm After Aneurysmal Subarachnoid Hemorrhage

Results of a Pilot Randomized Clinical Trial

Jo BS;
Allan H. F xander, MD;
C HS

Background subarachnoid hemorrha tes vasospasm after SAH

Methods—P s of symptom onset to r inotransferase, aspartate y evidence of hepatitis asospasm was defined a ephalus) in the presence n V_{MCA} >160 m/sec).

Results—Th ps. No patients developed decreased 3 to 10 days cerebral artery transcrani rsus 149±47; P<0.01). up (5 of 19) compared

Conclusion—The use of simvastatin as prophylaxis against delayed cerebral ischemia after aneurysmal SAH is a safe and well-tolerated intervention. Its use attenuates serum markers associated with brain injury and decreases the incidence of radiographic vasospasm and delayed ischemic deficit. (***Stroke*. 2005;36:2024-2026.**)

TABLE 2. Simvastatin Decreases Vasospasm

Measure	Simvastatin (n=19)	Placebo (n=20)	*P* Value
Transaminitis	11% (2/19)	5% (1/20)	NS
CPK elevation	5% (1/19)	0%	NS
Clinically significant myopathy or hepatic dysfunction	0	0	NS
Vasospasm	26% (5/19)	60% (12/20)	0.03
Highest mean V_{MCA}	103±41	149±47	0.006

Two patients in the simvastatin group and 1 patient in the placebo group developed transaminitis (AST or ALT >180 U/L). One patient in the simvastatin group had CPK elevation (CPK >1000 U/L).

Statin Use was not Associated with Less Vasospasm or Improved Outcome after Subarachnoid Hemorrhage

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Accepted, July 24, 2007.

OBJECTIVE: The development of delayed ischemia caused by cerebral vasospasm remains a common cause of morbidity and mortality after aneurysmal subarachnoid hemorrhage. Preliminary studies suggest that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) may decrease the risk of vasospasm, but additional study is required.

METHODS: Beginning in May 2006, our treatment protocol for patients presenting with subarachnoid hemorrhage was altered to routinely include the use of 80 mg of simvastatin per day for 14 days. Before this time, only patients with other indications for statins were treated. The charts of 203 consecutive patients over a period of 27 months were retrospectively reviewed, and 150 patients were included in the analysis, of whom 71 patients received statins. These patients were compared with 79 untreated patients to determine whether or not the use of statins was associated with a reduction in the occurrence of vasospasm, delayed infarction, or poor outcome (death, vegetative state, or severe disability).

RESULTS: Patients who were treated with statins and those who were not had similar baseline characteristics, although more patients in the former group were managed with endovascular coil embolization. There were no statistically significant differences in the proportion of patients developing at least moderate radiographic vasospasm (41% with statins versus 42% without, $P = 0.91$), symptomatic vasospasm (32% with statins versus 25% without, $P = 0.34$), delayed infarction (23% with statins versus 28% without, $P = 0.46$), or poor outcome (39% with statins versus 35% without, $P = 0.61$). After adjustment for differences in baseline characteristics, including the method of aneurysm treatment, statins were still not significantly protective.

CONCLUSION: The addition of statins to standard care was not associated with any reduction in the development of vasospasm or improvement in outcomes after aneurysmal subarachnoid hemorrhage. If there is a benefit to statin use, it may be smaller than suggested by previous studies. However, further randomized controlled trials are awaited.

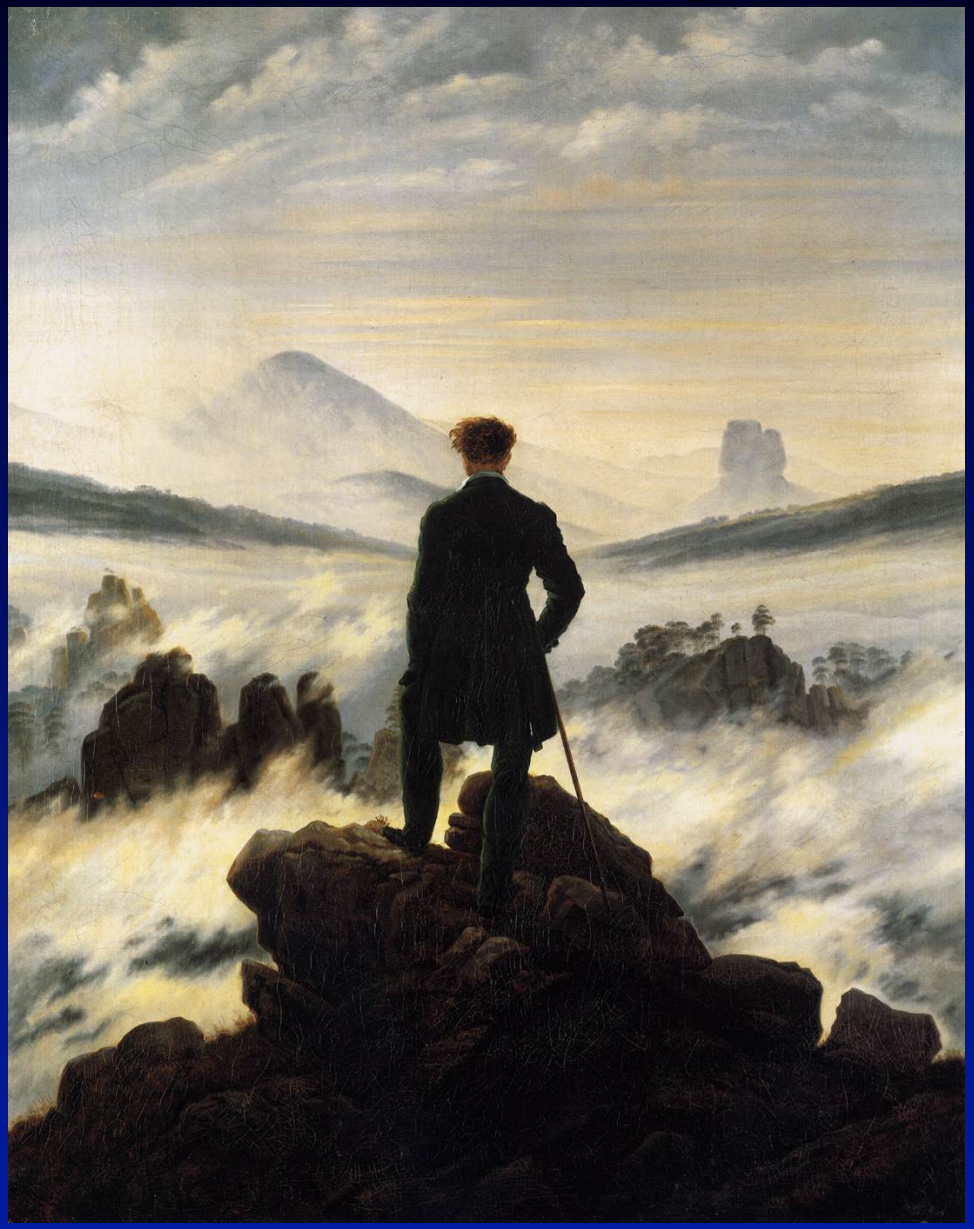
KEY WORDS: Cerebral aneurysm, Simvastatin, Statin, Subarachnoid hemorrhage, Transcranial Doppler, Vasospasm

Neurosurgery 62:422–430, 2008 DOI: 10.1227/01.NEU.0000297041.43986.5D www.neurosurgery-online.com

Despite recent advances in the care of patients with ruptured cerebral aneurysms, case fatality rates remain high, in the range of 35 to 50% (1, 6, 24, 25, 28). More than 40% of survivors experience long-term cognitive and functional limitations (7, 17). After the risk of recurrent hemorrhage has been minimized by securing the responsible aneurysm, the most important potential complications become the development of cerebral vasospasm and delayed ischemia, which typically occur 4 to 14 days after the ictus. Angiographic evidence of vasospasm is observed in as many as two-thirds of the patients, and clinical manifestations occur in 20 to 30%, of whom more than 50% develop infarction (6, 12, 15, 16, 22). The only pharmacological agent proven to be beneficial is the calcium channel blocker nimodipine, but its effect is modest and the mechanism uncer-

1. **Symptomatic vasospasm:**
   - 32% vs. 25% control
2. **Radiographic vasospasm:**
   - 41% vs. 42% control
3. **Poor outcomes:**
   - 39% vs. 35% control

Future Directions in Vasospasm Therapy



Wanderer Above the Mist (1818) by Caspar David Friedrich (1774-1840)

Inflammatory Etiology of Vasospasm after SAH: Early Indirect Evidence

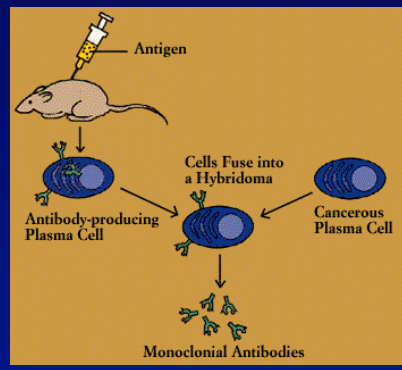
1. Higher systemic temperatures in patients with VSP
   - Rousseaux P et al., ***Surg Neurol*** 14: 459, 1980

2. Macrophages and granulocytes in walls of vessels in VSP
   - Crompton MR, ***Brain*** 87: 491, 1964
   - Hughes JT, Schianchi PM, ***J Neurosurg*** 48: 515, 1978

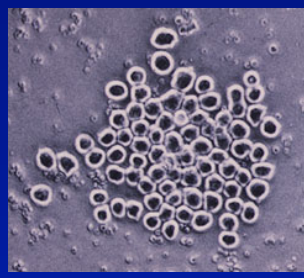
3. Increased levels of "immunoglobulins" and "complement components" in serum of patients with VSP
   - Pellettieri L et al., ***Experientia*** 37: 1170, 1981
   - Pellettieri L et al., ***Neurosurgery*** 19: 767, 1986

Inflammatory Etiology of Vasospasm after SAH: The Advent of Molecular Evidence

1. Creation of monoclonal antibodies (MAbs)
   - Kohler G and Milstein C,
     Nature 256: 495, 1975

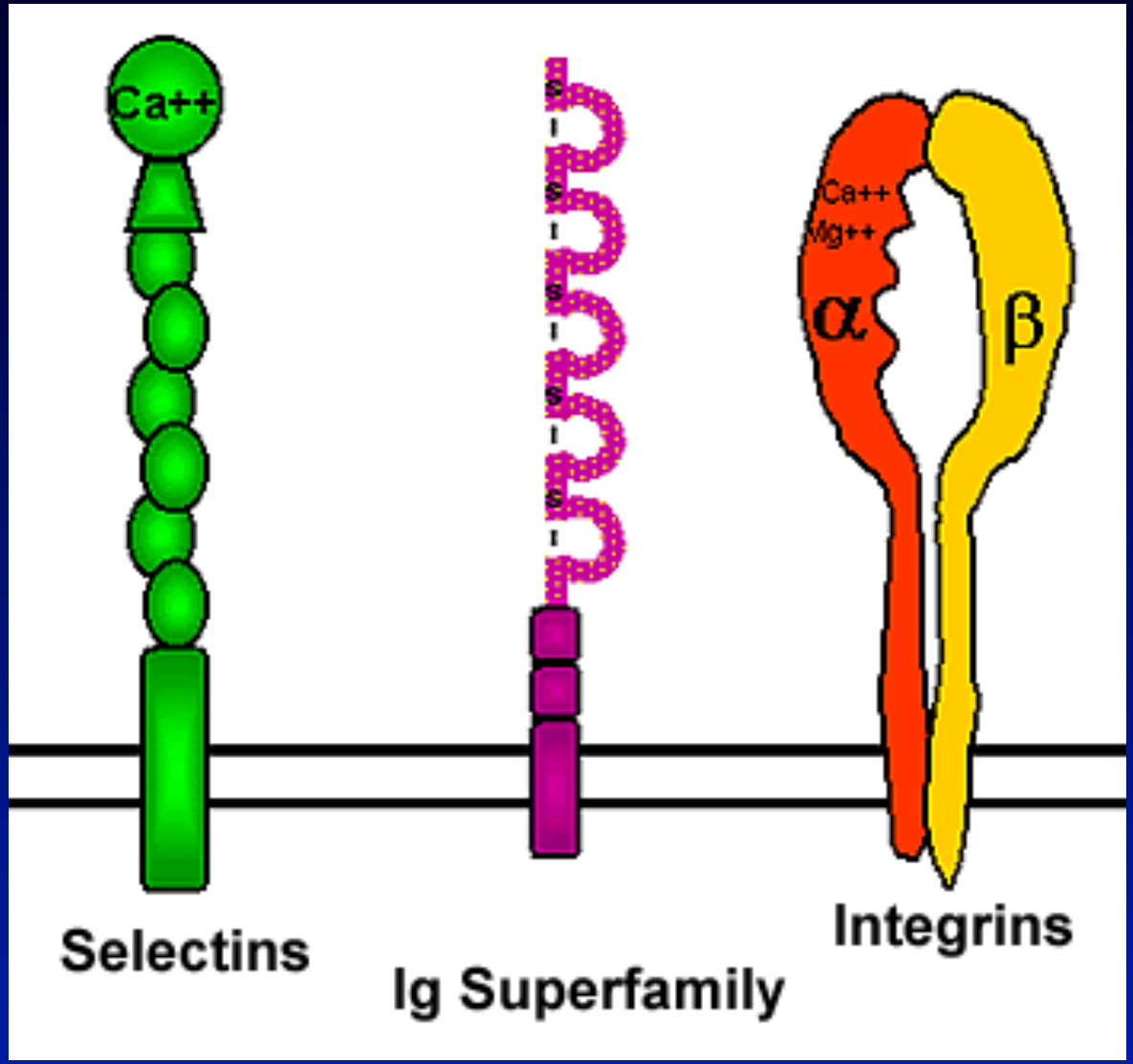


2. Description of cell adhesion molecules (CADs)
   - Earliest descriptions in 1985
   - Selectins, integrins, Ig superfamily



3. The "three-step" paradigm of leukocyte and endothelial cell interactions mediated by CAMs in inflammation
   - Springer TA, ***Cell*** 76: 301, 1994

The Major Families of Cell Adhesion Molecules

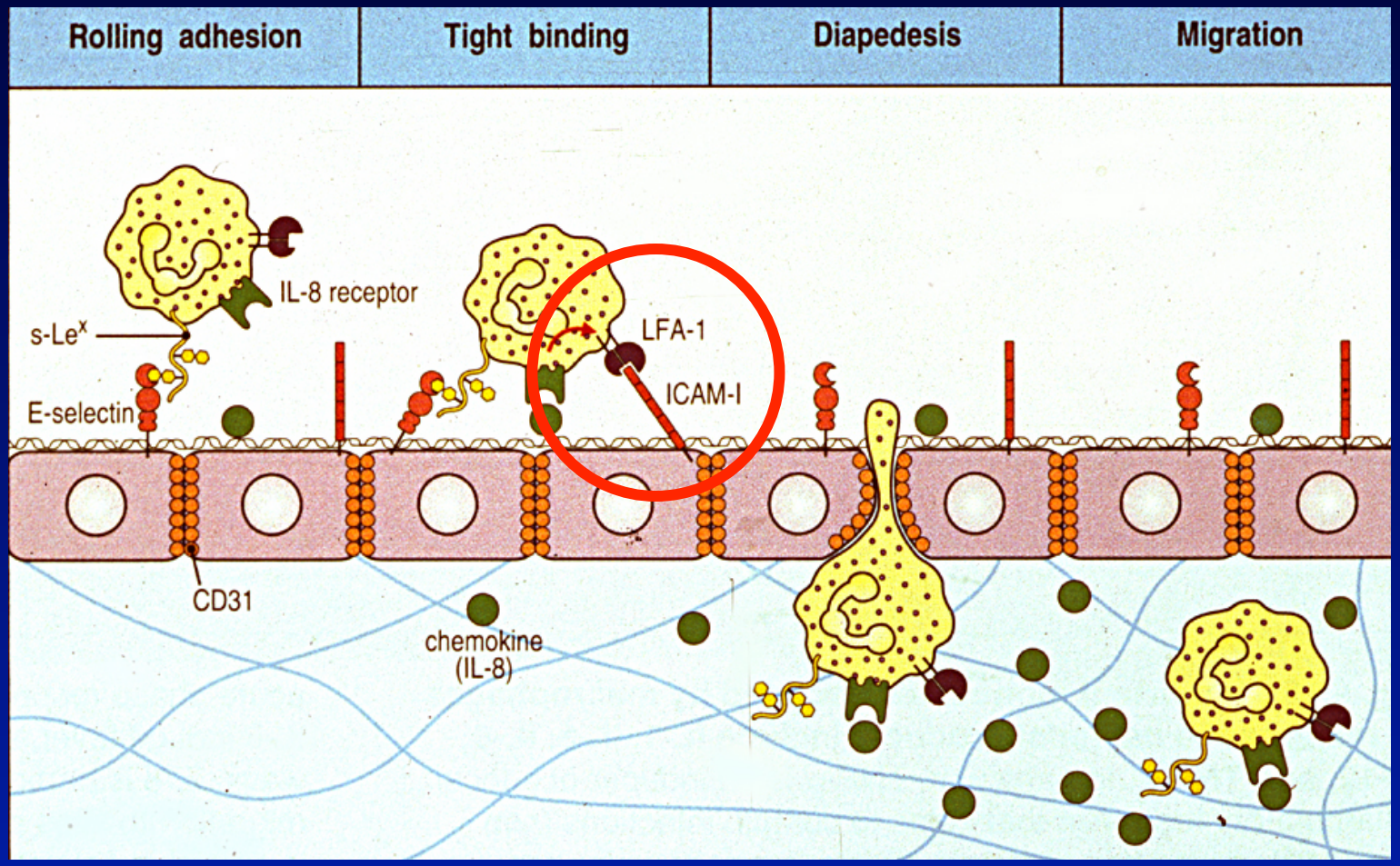


Major Members of the Selectins, Integrins, and Ig Superfamily

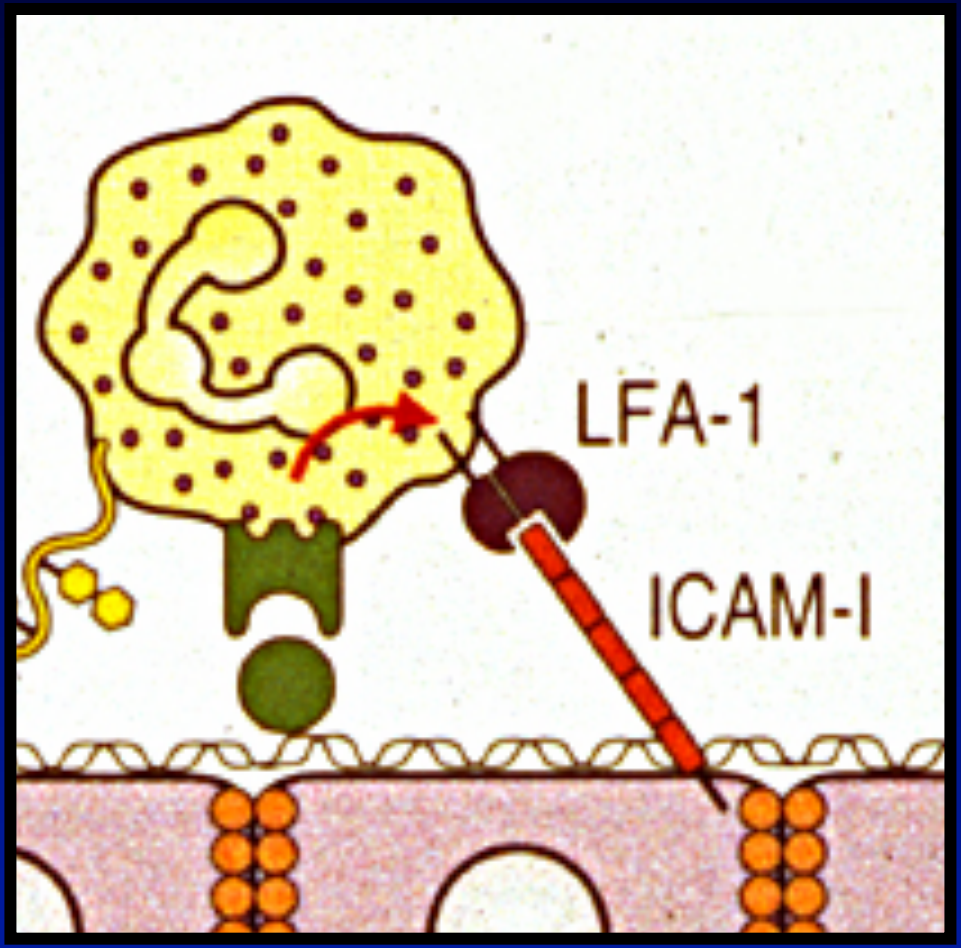
		Name	Tissue distribution	Ligand
Selectins	P-selectin	P-selectin (PADGEM, CD62P)	Activated endothelium and platelets	PSGL-1, sialyl-Lewis^x
Bind carbohydrates. Initiate leukocyte–endothelial interaction		E-selectin (ELAM-1, CD62E)	Activated endothelium	Sialyl-Lewis^x
Integrins	LFA-1	$\alpha_L\beta_2$ (LFA-1, CD11a/CD18)	Monocytes, T cells, macrophages, neutrophils, dendritic cells	ICAMs
Bind to cell-adhesion molecules and extracellular matrix. Strong adhesion		$\alpha_M\beta_2$ (Mac-1, CR3, CD11b/CD18)	Neutrophils, monocytes, macrophages	ICAM-1, iC3b, fibrinogen
		$\alpha_X\beta_2$ (CR4, p150.95, CD11c/CD18)	Dendritic cells, macrophages, neutrophils	iC3b
		$\alpha_5\beta_1$ (VLA-5, CD49d/CD29)	Monocytes, macrophages	Fibronectin
Immunoglobulin superfamily	ICAM-1	ICAM-1 (CD54)	Activated endothelium	LFA-1, Mac1
Various roles in cell adhesion. Ligand for integrins		ICAM-2 (CD102)	Resting endothelium, dendritic cells	LFA-1
		VCAM-1 (CD106)	Activated endothelium	VLA-4
		PECAM (CD31)	Activated leukocytes, endothelial cell–cell junctions	CD31

"Three-Step" Paradigm of Leukocyte-Endothelial Cell Binding at the Site of Inflammation:

I. Rolling adhesion II. Chemoattraction III. Tight Binding/Migration



Critical Integrin-Ig Superfamily Interactions: LFA-1 or Mac-1 Binding to ICAM-1

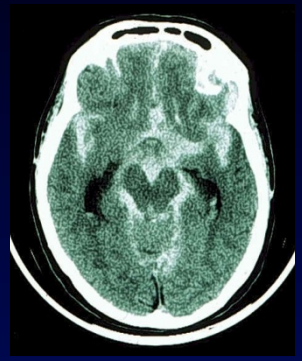


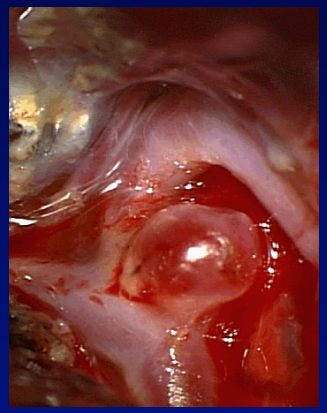
Unanswered Questions in Vasospasm

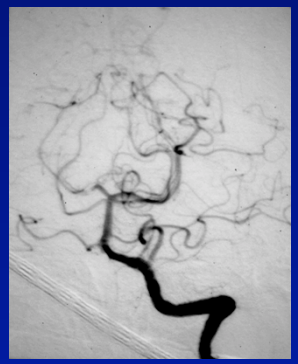
1. Main focus of clinical and basic research
   - Arterial narrowing

2. Unexplained clinical phenomena
   - Only 33% of patients develop symptomatic vasospasm
   - Cerebral ischemia
     Arterial narrowing and ischemia are not linked
   - Meningitis syndrome
     Fever, elevated peripheral WBC, CNS "irritation"
   - Edema
   - Neurogenic myocardial dysfunction
   - Neurogenic pulmonary edema
   - Cerebral salt wasting

3. Unexplained observation in animal models of SAH
   - Although animals develop vasospasm, they typically do not have ischemic deficits







Erythrocytes (RBCs) and Hemoglobin (Hgb)

1. An average human makes
   3 million RBCs per second
   (260 billion RBCs per day)

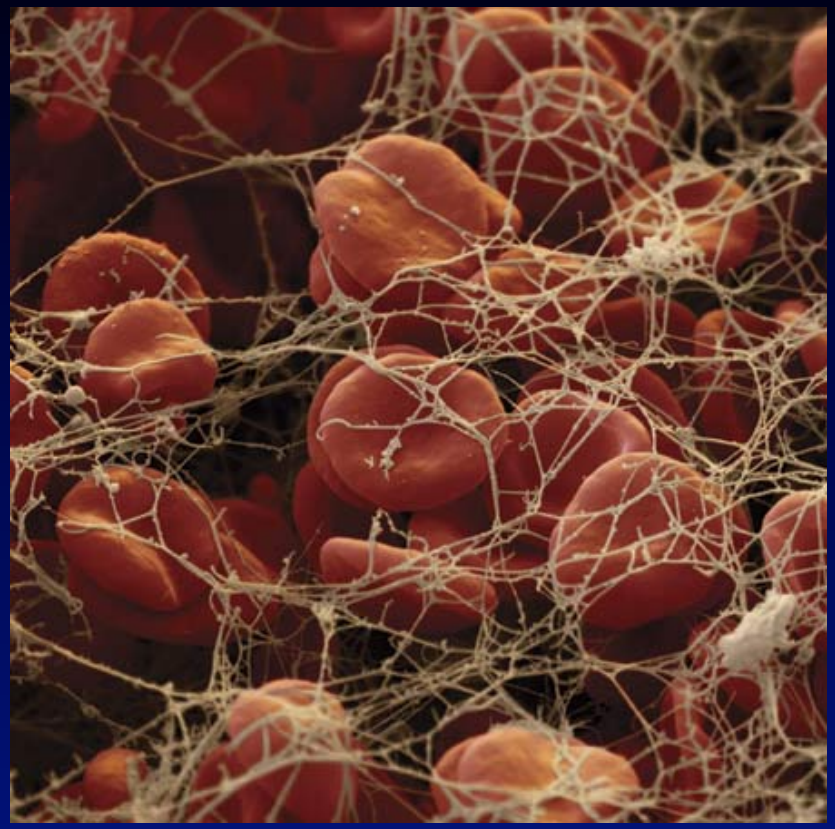
2. RBCs are destroyed and removed from the circulation at the same rate

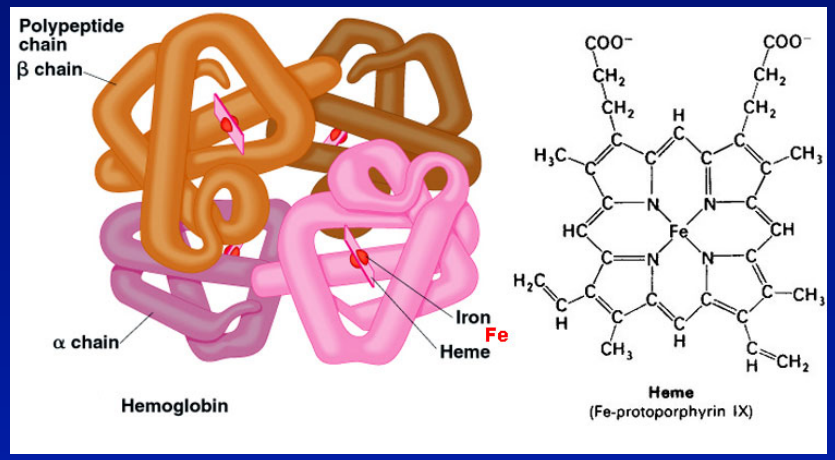
3. Free ("extracorpuscular") Hgb is highly toxic

4. Recycling of RBCs and neutralization of Hgb is a major continuous function carried out primarily by macrophages

5. Haptoglobin binds Hgb and presents it to macrophages with CD163 receptor for phagocytosis

"CD163: A regulated hemoglobin scavenger receptor with a role in the anti-inflammatory response"
S. K. Moestrup and H. J. Moller *Ann Med* 36: 347-354, 2004
(University of Aarhus, Denmark)





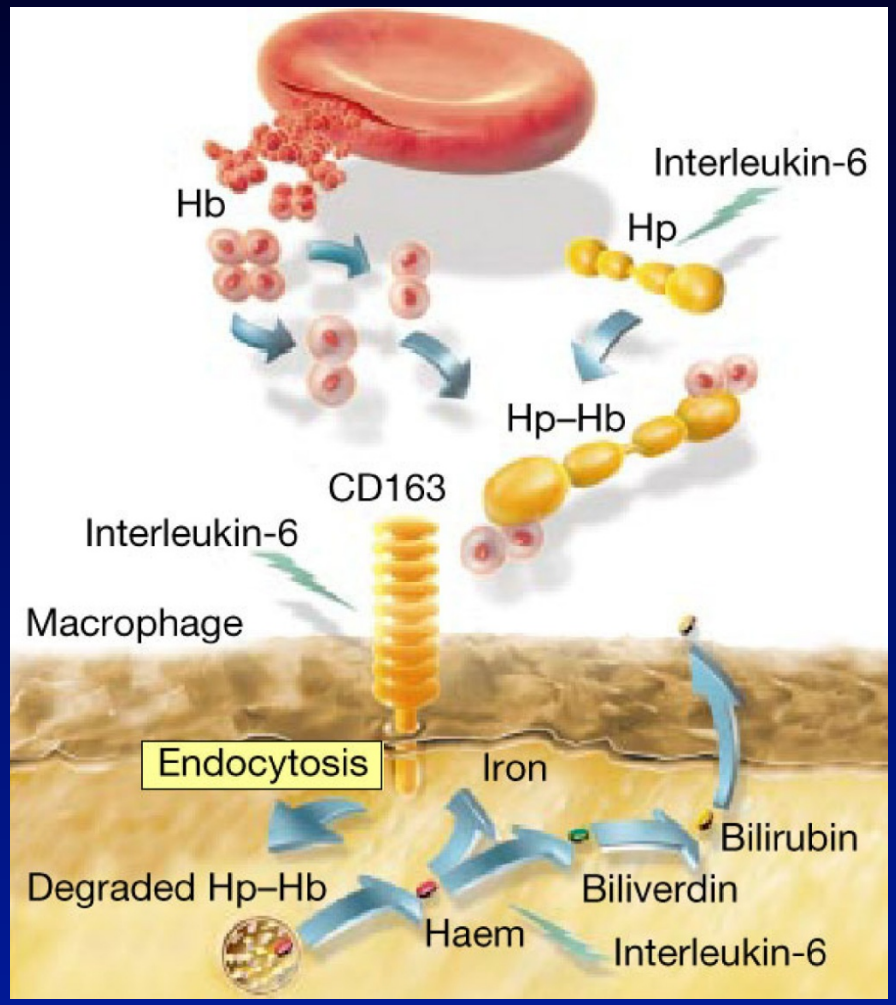
Role of Haptoglobin (Hp) in Hemoglobin (Hgb) Metabolism

1. Extracorpuscular Hgb is toxic

2. **Haptoglobin** is:
   - a serum protein made up of two alpha and two beta chains connected by disulfide bridges
   - produced mostly by hepatocytes

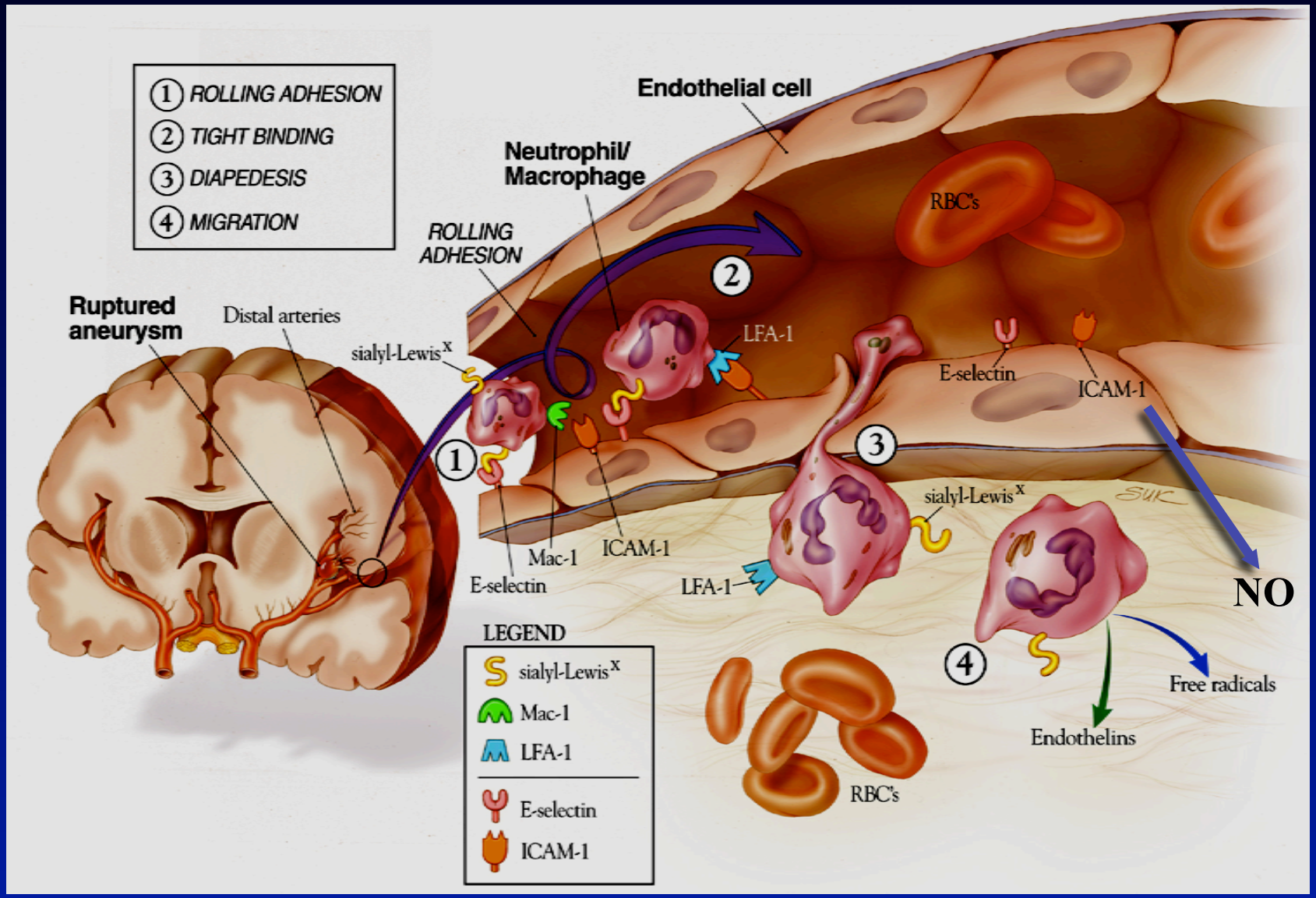
3. Haptoglobin binds free Hgb and presents it to macrophages for phagocytosis (CD163 receptor)

4. Haptoglobin reduces inflammation caused by free Hgb by facilitating macrophage phagocytosis



Dennis C. Nature 409: 141, 2001

Clinical observations and current molecular research suggest that inflammation, i.e., leukocyte-endothelial cell interactions, may be the root cause of chronic vasospasm after SAH



G. L. Gallia and R. J. Tamargo *Neurological Research* 28: 750-758, 2006

How do either macrophages or neutrophils induce vasospasm after entering the subarachnoid space?

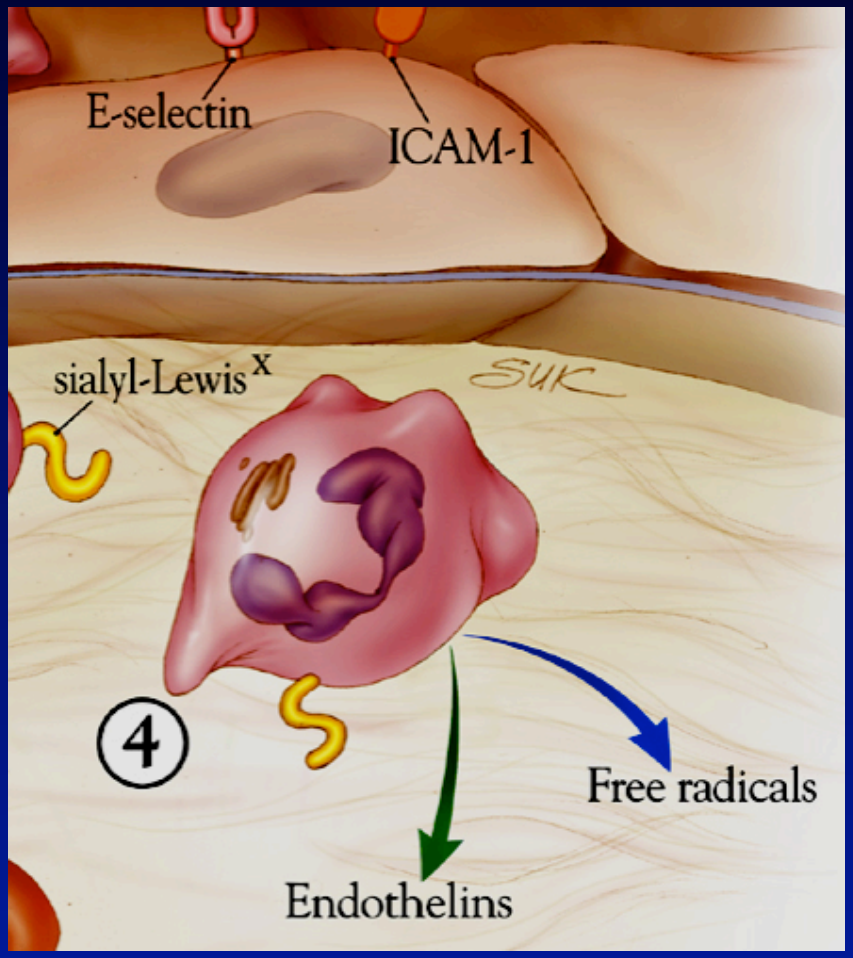
"Endothelins, peptides with potent vasoactive properties, are produced by human macrophages"
Ehrenreich H et al., ***J Exp Med*** 172: 1741, 1990

"Activated neutrophils inhibit cerebrovascular endothelium-dependent relaxations in vitro"
Csaki C et al., ***Life Sci*** 49: 1087, 1991

"The endothelium-dependent relaxation of human middle cerebral artery: Effect of activated neutrophils"
Akopov SE et al., ***Experientia*** 48: 34, 1992

"Endothelin-1 in subarachnoid hemorrhage: An acute-phase reactant produced by CSF leukocytes"
Fasbender K et al., ***Stroke*** 31: 2971, 2000

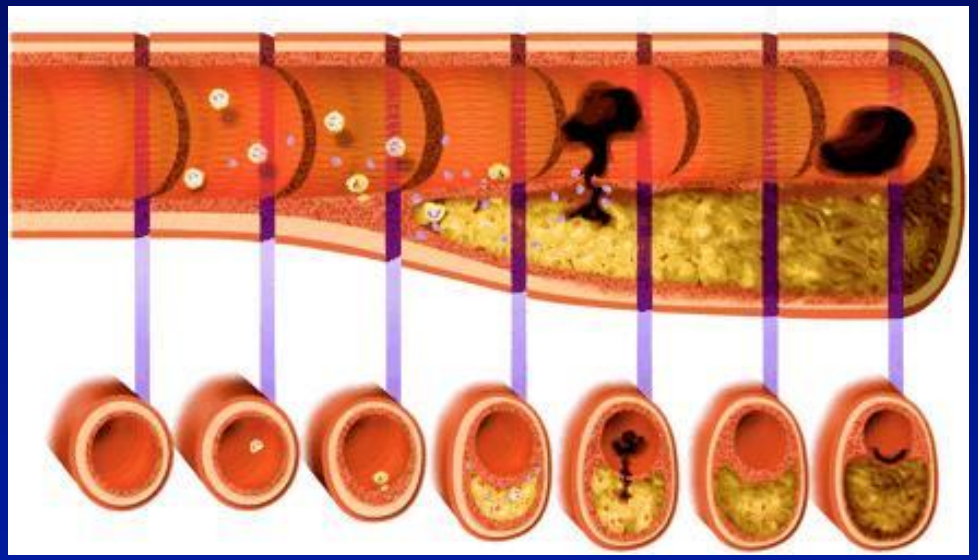
"The biosynthesis of endothelin-1 by human polymorphonuclear leukocytes"
Sessa WC et al., ***Biochem Biophys Res Commun*** 174: 613, 1991

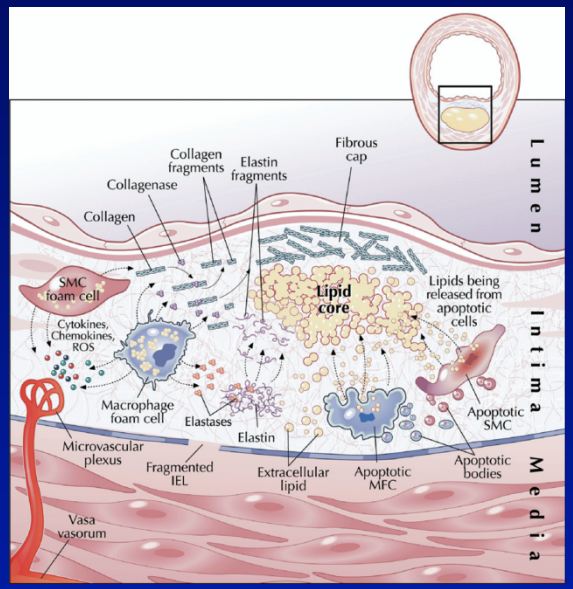


Increasing recognition of the role of inflammation in many diseases

Table 1 *Review/Expanded Inflammatory Hypothesis*
Evidence for persistent tissue and systemic cytokine expression in chronic progressive diseases

Disease	↑ Tissue Cytokines	↑ Serum Markers	Specific Findings
Coronary disease	x	x	Predicts ↑ risk at every clinical phase
Diabetes	x	x	TNF → insulin resistance and β-cell death
AD	x	x	Marked ↑ in neurofibrillary tangles
Multiple sclerosis	x	x*	Induces animal model of multiple sclerosis
Cirrhosis	x	x	Increased in tissue, independent of cause
Osteoporosis	x	x	Induces animal mode of osteoporosis
Chronic pancreatitis	x	x	Localized in islands of abnormal pancreas
Pulmonary fibrosis	x	x	TNF → alveolar injury, fibroblastic foci
Glomerulosclerosis	x	x	TGF-β overexpression in fibrotic regions



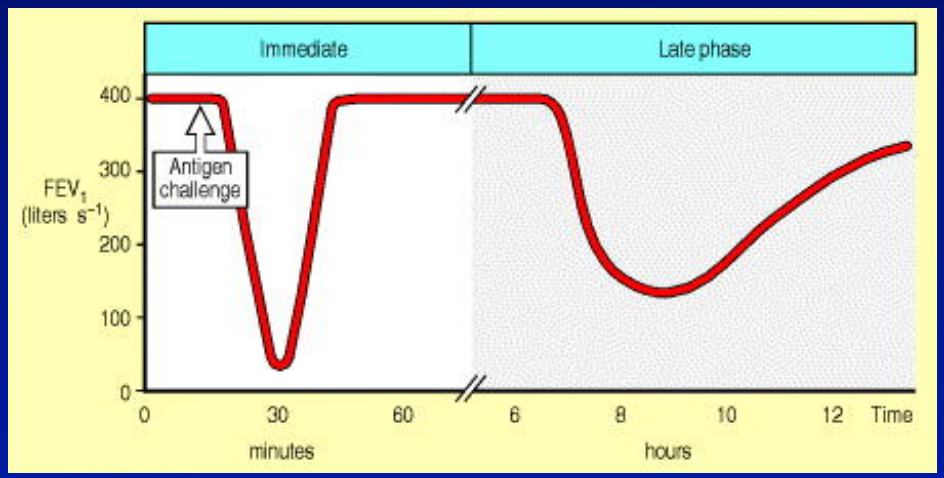


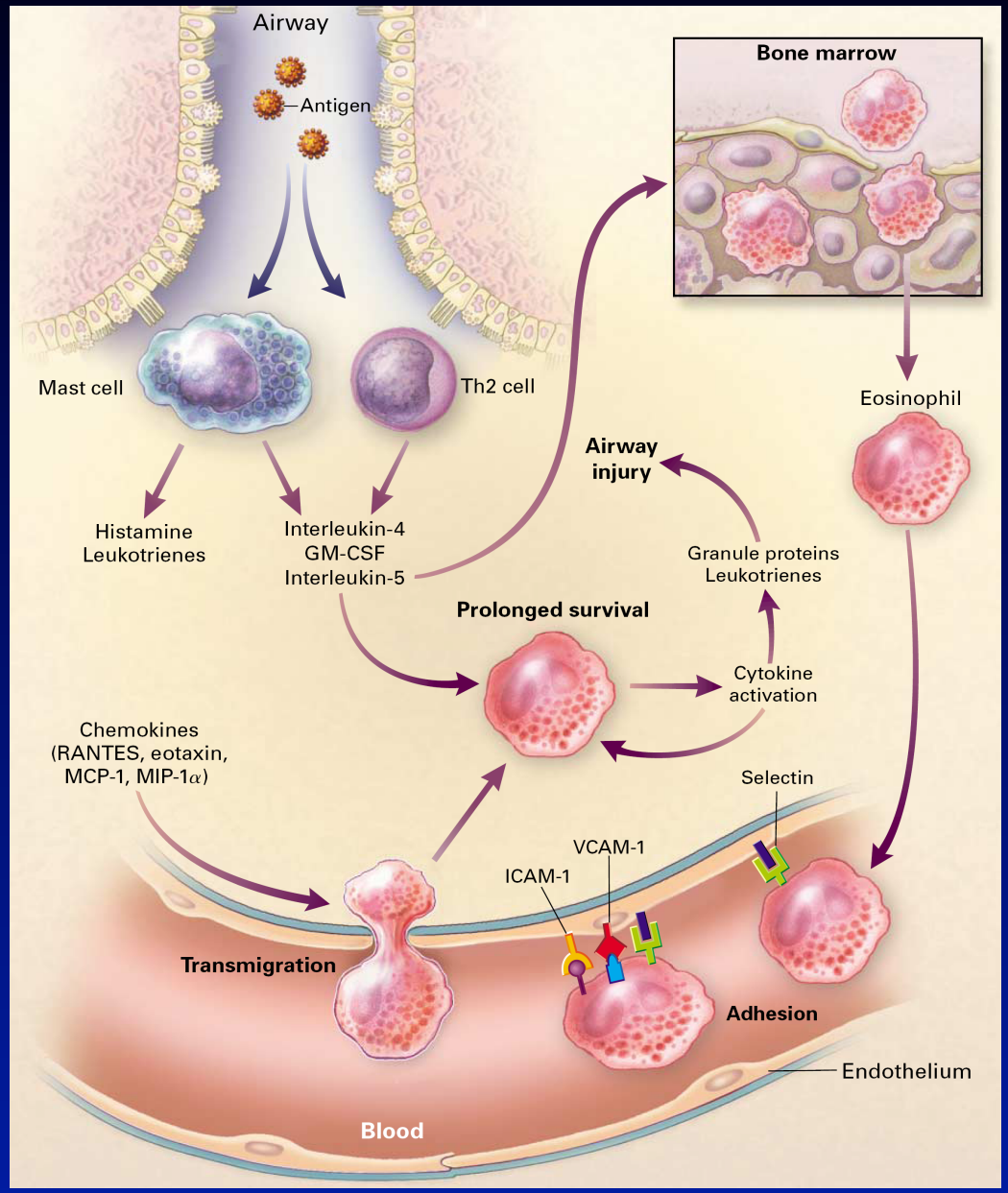
Libby P, Ridker PM. "Inflammation and atherothrombosis." J Am Coll Cardiol 48: A33, 2006; Forrester JS, Libby P. Am J Cardiol 99: 732, 2007

Asthma: An Inflammatory Disease

1. Initially was thought to be a disease of the bronchial musculature and was treated primarily with bronchodilators

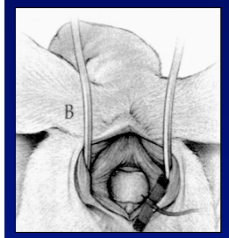
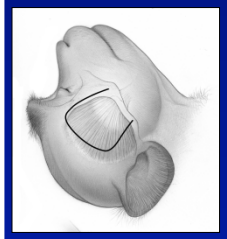
2. Asthma is currently viewed as primarily an inflammatory disorder with secondary bronchoconstrictive, muscular changes.



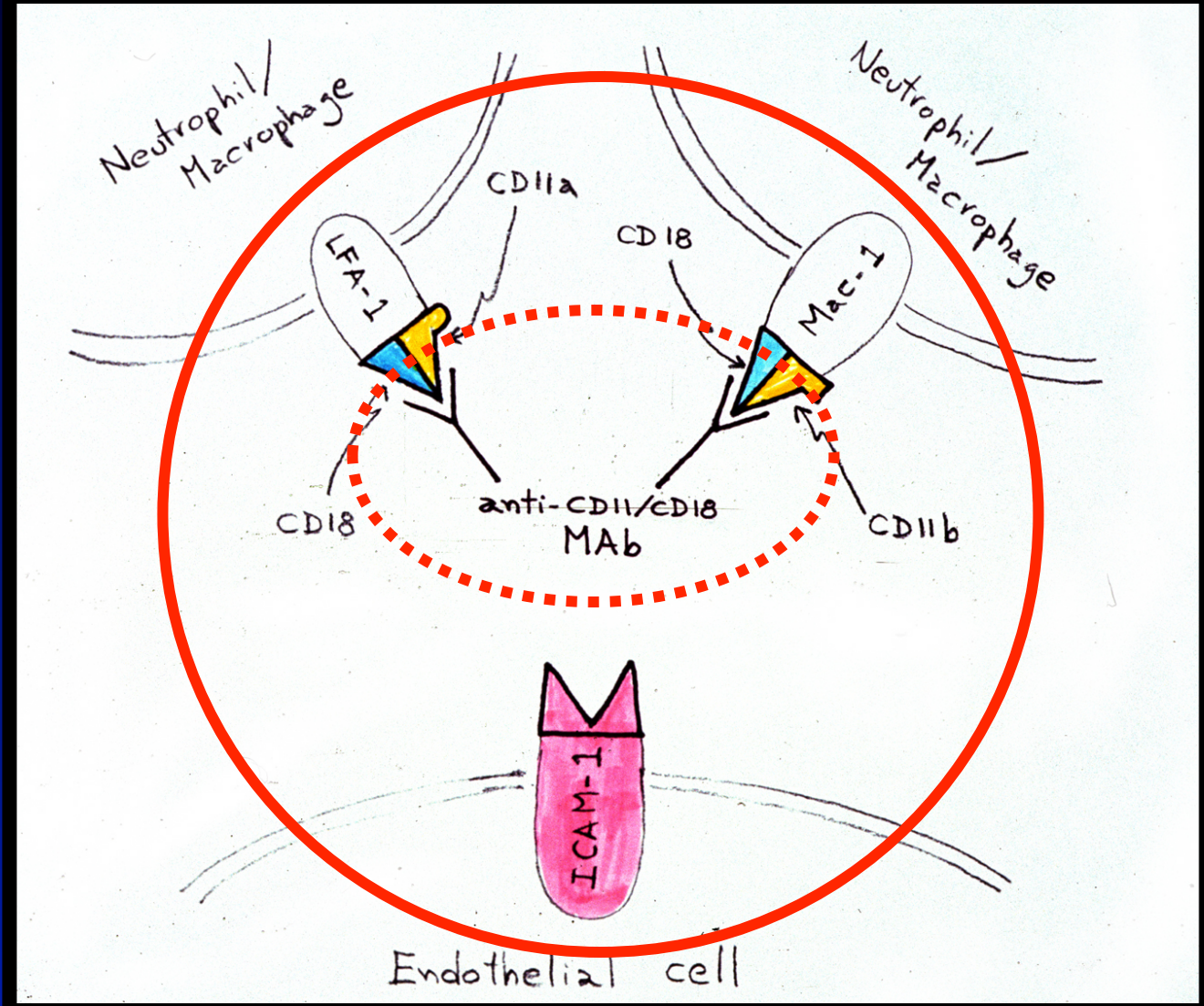


Busse WW, Lemansky RF. "Advances in Immunology: Asthma." NEJM 344: 350, 2001

Overview of Evidence Supporting the Role of Leukocyte-Endothelial Cell Interactions and Endothelins/NO in Vasospasm

	MAb against CAMs	Ibuprofen	Nitric Oxide
	E. Oshiro et al. ***Stroke*** *28: 2031, 1997* R. Clatterbuck et al. ***Jl Nus*** *97: 676, 2002* (Anti-ICAM-1, LFA-1)	Q.-A. Thai et al. ***Stroke*** *30: 140, 1999* (Ibuprofen in EVAc)	T. Tierney et al. ***Nus*** *49: 945, 2001* (DETA/NO in EVAc)
	G. Pradilla et al. ***Jl Nus*** *101: 88, 2004* (Anti-CD11/CD18)	J. Frazier et al. ***Jl Nus*** *101: 93, 2004* (Ibuprofen in EVAC)	P. Gabikian et al. ***Stroke*** *33: 2681, 2002* G. Pradilla et al. ***Nus*** *55: 1393, 2004* (DETA/NO in EVAc)
	R. Clatterbuck et al. ***Jl Nus*** *99: 376, 2003* (Anti-CD11/CD18)	G. Pradilla et al. ***Nus*** *57(1): 184, 2005* (Ibuprofen in EVAc)	R. Clatterbuck et al. ***Jl Nus*** *103:745, 2005* (DETA/NO in EVAc)

Critical Integrin-Ig Superfamily Interactions: LFA-1 or Mac-1 Binding to ICAM-1



Journal of Neurosurgery 101: 88-92, 2004

Prevention of vasospasm following subarachnoid hemorrhage in rabbits by anti-CD11/CD18 monoclonal antibody therapy

Gustavo Pradilla, M.D., Paul P. Wang, M.D., Federico G. Legnani, M.D., Lynn Ogata, Ph.D., Gregory N. Dietsch, Ph.D., and Rafael J. Tamargo, M.D.

Department of Neurosurgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland; Ospedale San Gerardo, Monza, Italy; and ICOS Corporation, Bothell, Washington

- Rabbits (n=26)
- Treatment with anti-CD11/CD18 MAb vs. control MAb
- Animals sacrificed 72 hrs after SAH
- Anti-CD11/CD18 MAb prevents vasospasm

Journal of Neurosurgery 99: 376-382, August 2003

Prevention of cerebral vasospasm by a humanized anti-CD11/CD18 monoclonal antibody administered after experimental subarachnoid hemorrhage in nonhuman primates

Richard E. Clatterbuck, M.D., Ph.D., Philippe Gailloud, M.D., Lynn Ogata, Ph.D., Abeyu Gebremariam, Gregory N. Dietsch, Ph.D., Kieran J. Murphy, M.D., and Rafael J. Tamargo, M.D.

Department of Neurological Surgery and Division of Interventional Neuroradiology, The Johns Hopkins University School of Medicine, Baltimore, Maryland; and ICOS Corporation, Bothell, Washington

- Monkeys (n=6)
- Treatment with anti-CD11/CD18 MAb vs. control MAb
- Angiography repeated on POD 7
- Anti-CD11/CD18 MAb prevents vasospasm

Stroke 28: 2031-2038, October 1997

Inhibition of Experimental Vasospasm With Anti–Intercellular Adhesion Molecule-1 Monoclonal Antibody in Rats

Eric M. Oshiro, MD; Patricia A. Hoffman, MS; Gregory N. Dietsch, PhD; Mark C. Watts, MD; Drew M. Pardoll, MD, PhD; Rafael J. Tamargo, MD

- Rats (n=36, 72 arteries, and n=7, 14 arteries)
- Treatments with anti-ICAM-1 MAb vs. control MAb
- Animals sacrificed at 12 days
- Macrophage/granulocyte infiltration quantitated at 24 hrs
- Anti-ICAM-1 MAb prevents vasospasm and leukocyte infiltration

Journal of Neurosurgery 97: 676-682, September 2002

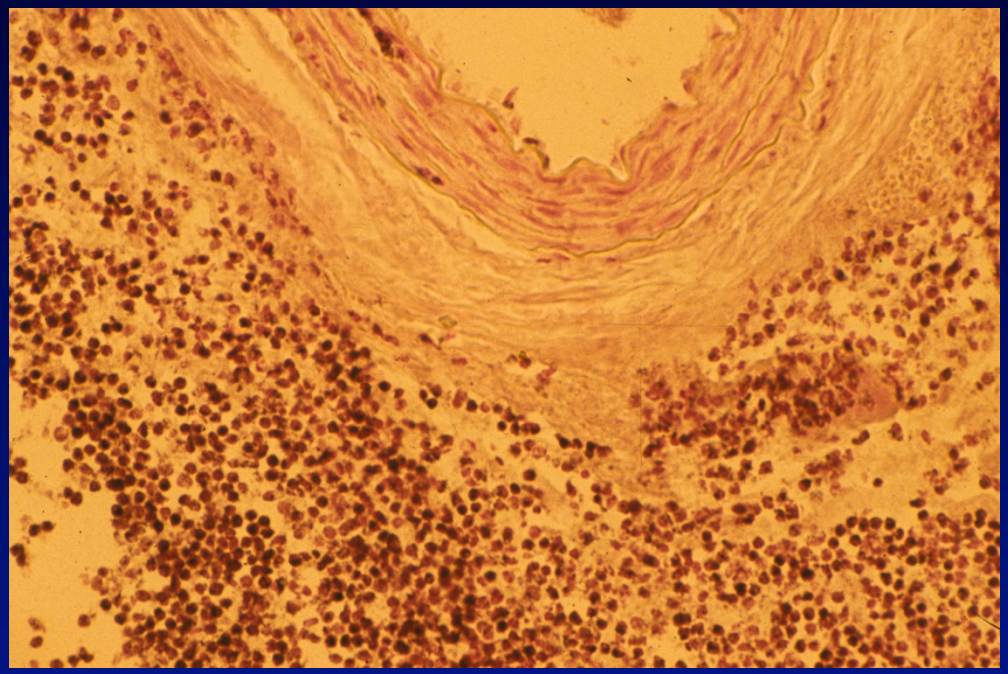
Inhibition of vasospasm with lymphocyte function-associated antigen–1 monoclonal antibody in a femoral artery model in rats

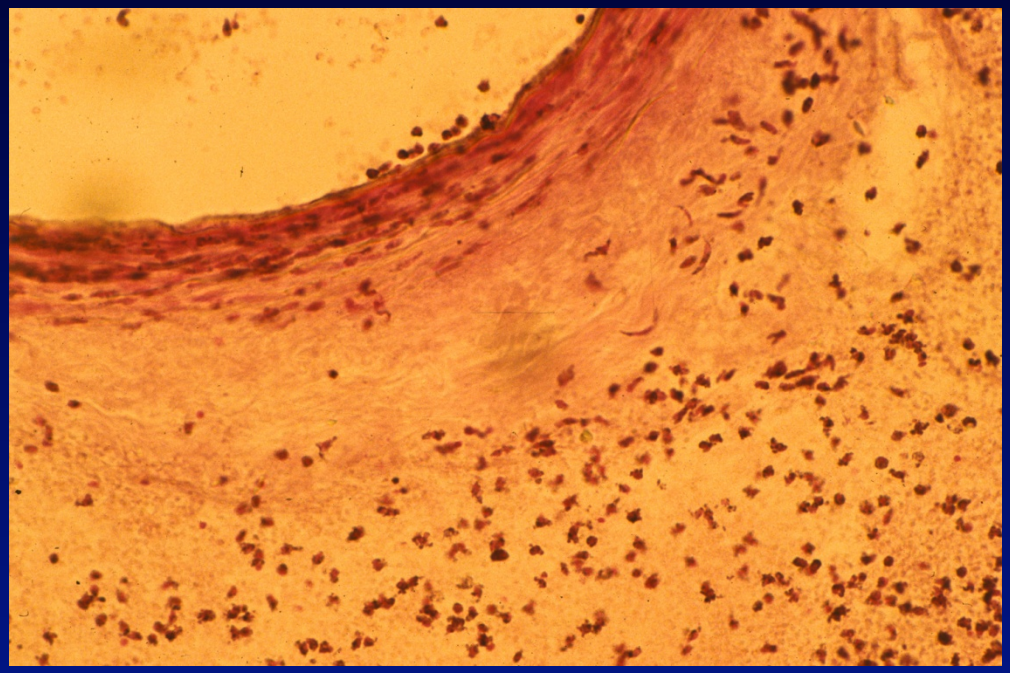
Richard E. Clatterbuck, M.D., Ph.D., Eric M. Oshiro, M.D., Patricia A. Hoffman, M.S., Gregory N. Dietsch, Ph.D., Drew M. Pardoll, M.D., Ph.D., and Rafael J. Tamargo, M.D.

Departments of Neurosurgery, and Molecular Biology and Genetics, The Johns Hopkins University School of Medicine, Baltimore, Maryland; and ICOS Corporation, Bothell, Washington

- Rats (n=38, 76 arteries, and n=9, 18 arteries)
- Treatments with anti-ICAM-1, anti-LFA-1, and control Mabs
- Animals sacrificed at 12 days
- Macrophage/granulocyte infiltration quantitated at 24 hrs
- Anti-ICAM-1 and anti-LFA-1 treatments prevent vasospasm and reduce leukocyte infiltration

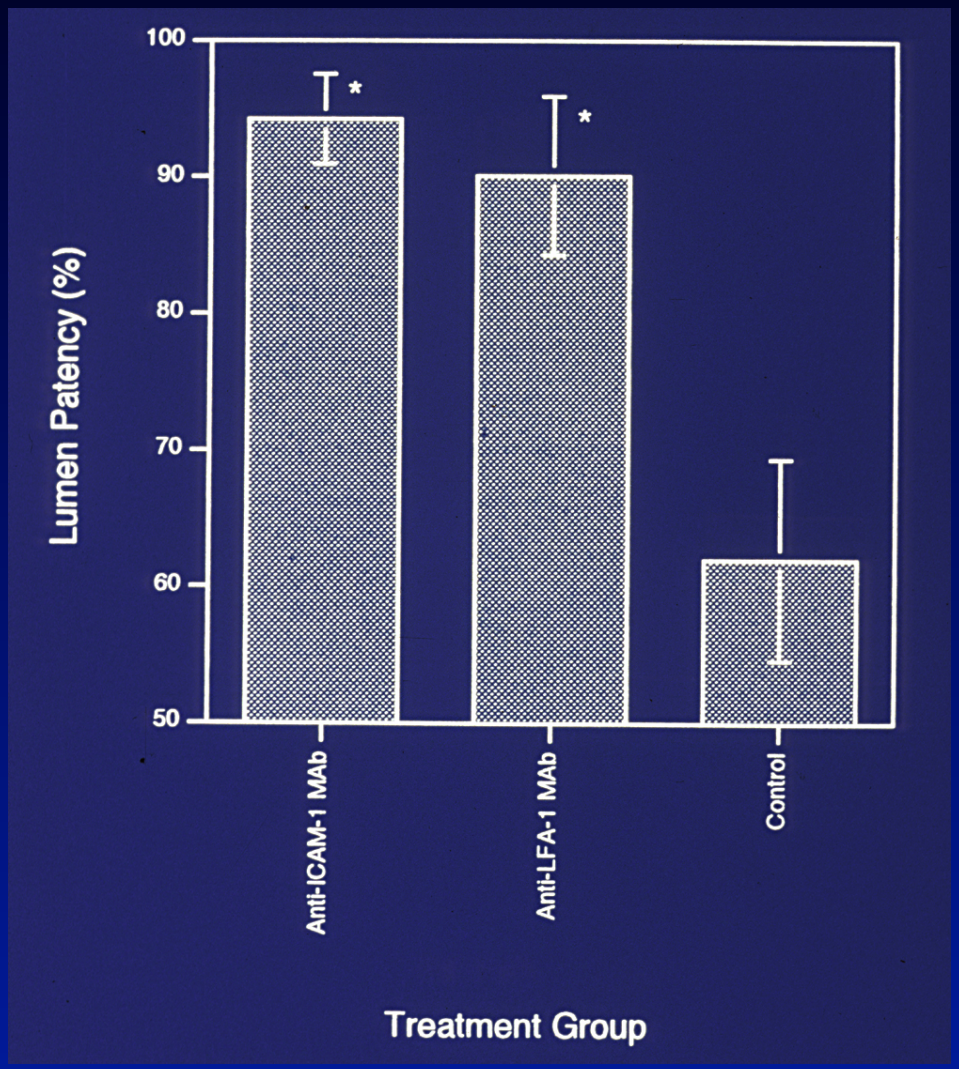
Granulocyte/Macrophage Infiltration (OX-41 Immunohistochemistry)

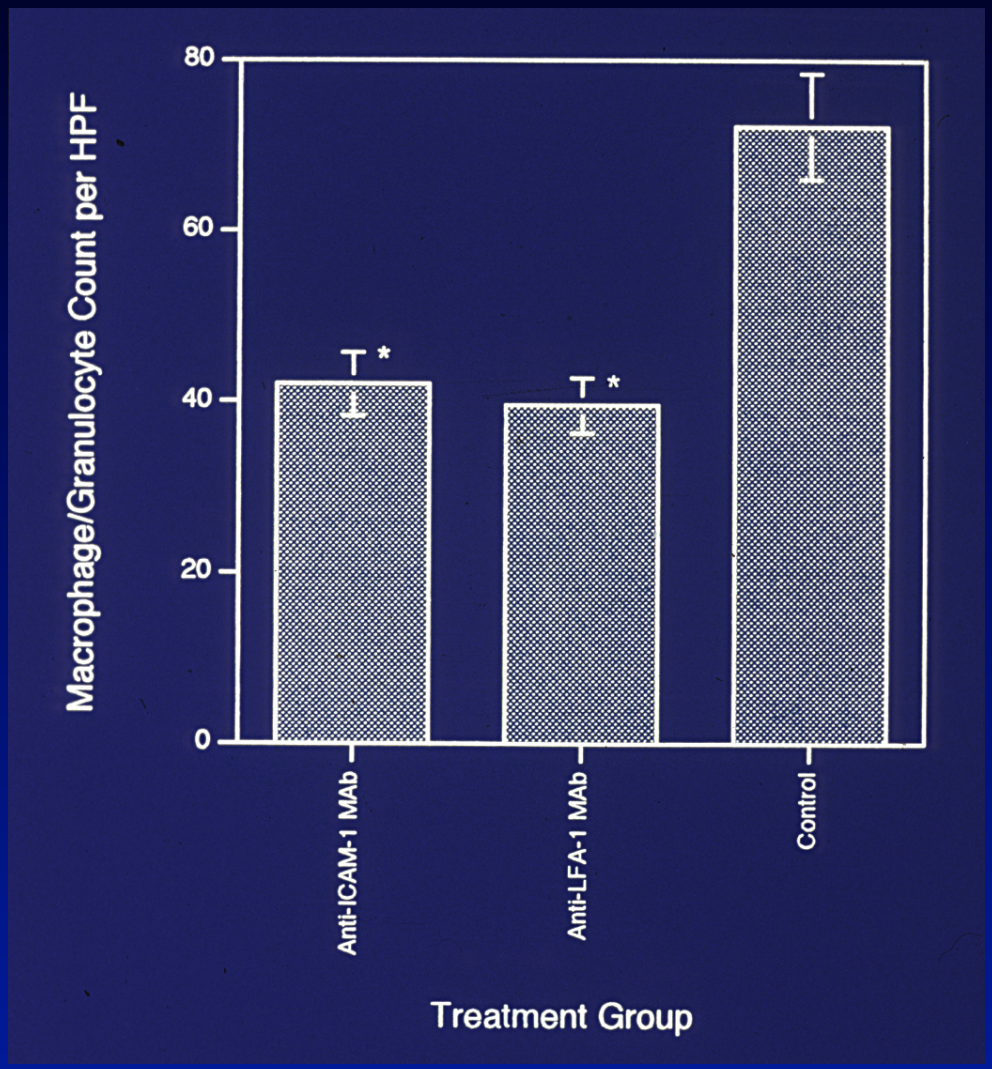




Femoral arteries 24 hrs after blood deposition treated with either control MAb (left) or anti-ICAM-1 MAb (right)

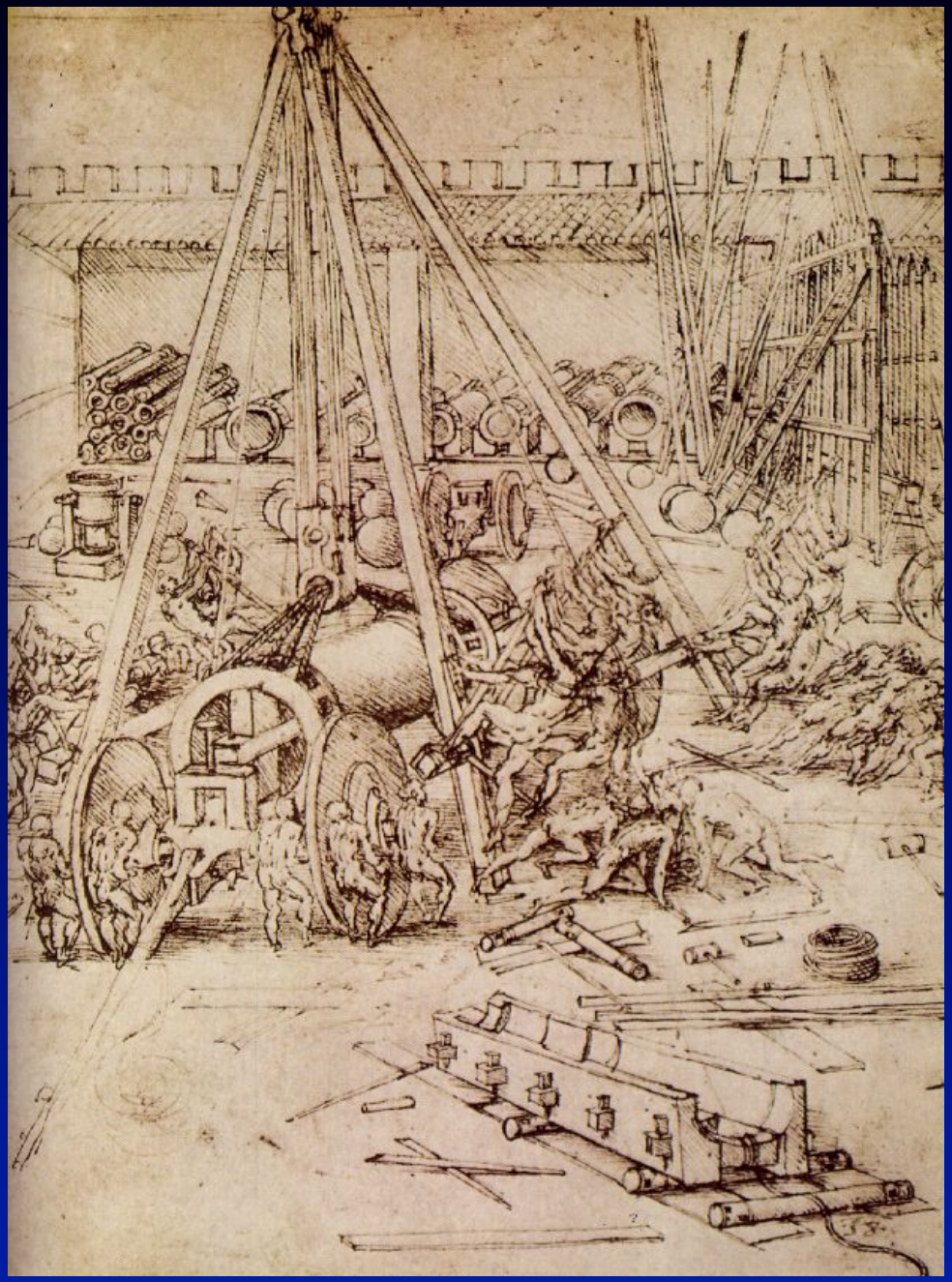
Results of Anti-ICAM-1 and anti-LFA-1 MAb Therapy





Lumen patencies (%)

Macrophage/Granulocyte Counts



Delayed treatment of vasospasm with ibuprofen

1. The results of the delayed treatment (after 24 hours from hemorrhage), however, were disappointing.

2. Anti-inflammatory therapy works only if initiated within 12 hours after SAH.

3. For delayed treatment of vasospasm (which is clinically more important) a different strategy was sought.

Journal of Neurosurgery 101: 93-98, 2004

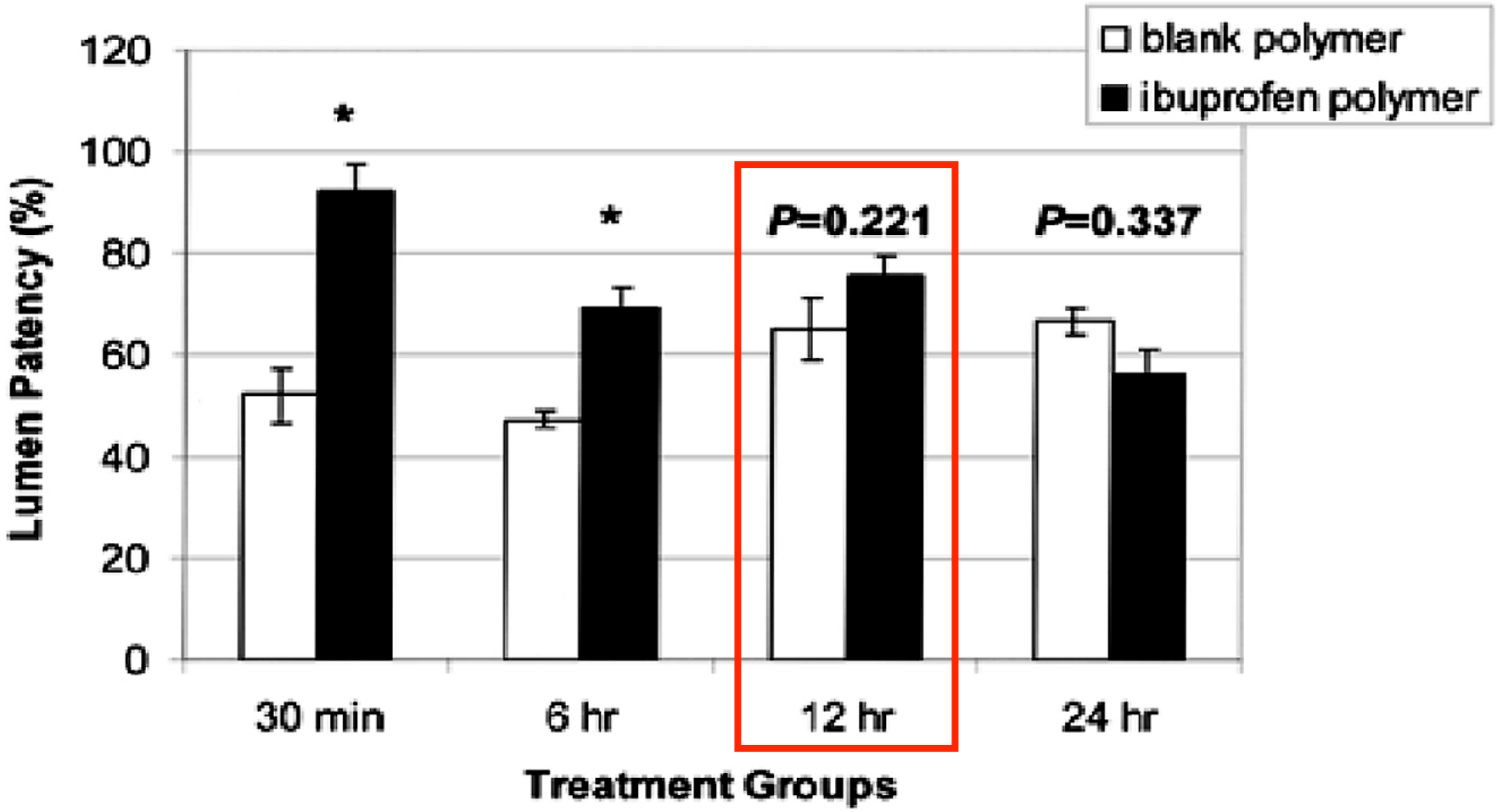
Inhibition of cerebral vasospasm by intracranial delivery of ibuprofen from a controlled-release polymer in a rabbit model of subarachnoid hemorrhage

JAMES L. FRAZIER, M.D., GUSTAVO PRADILLA, M.D., PAUL P. WANG, M.D., AND RAFAEL J. TAMARGO, M.D.

Department of Neurological Surgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland

- Rabbits (n=54)
- Ibuprofen incorporated into controlled-release polymers (EVAc)
- Treatments at 30 min, 6, 12, or 24 hr after SAH
- Animals sacrificed at 72 hr and basilar arteries measured
- Treatment at 30 min or 6 hr prevented vasospasm

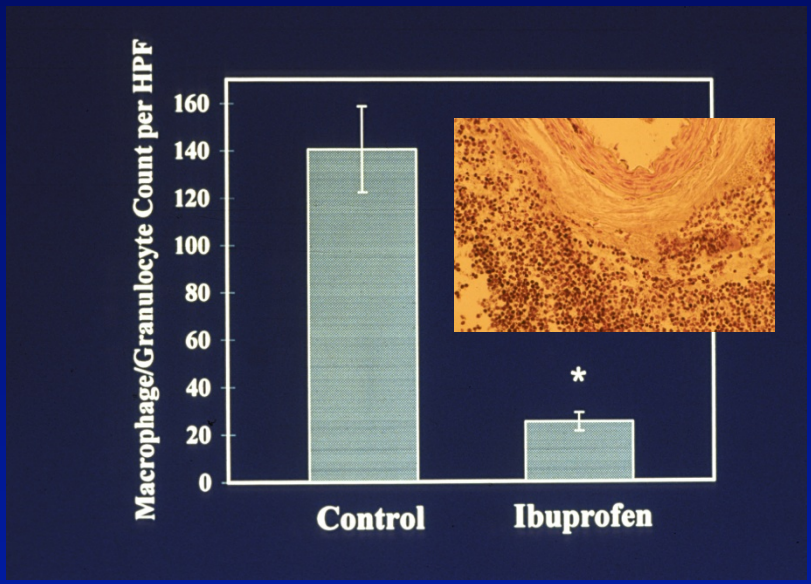
Ibuprofen-EVAc Treatment and Vasospasm in Rabbits



Why doesn't delayed (>12 hours) ibuprofen treatment prevent vasospasm?

1. ICAM-1 expression (and thus macrophage/granulocyte migration) occurs 3-24 hours after blood deposition

2. Critical levels of peri-adventitial macrophages/granulocytes reached by 12 hours



Time after pouch placement	Blood-exposed Arteries	Saline-exposed Arteries
1 h	+	+
3 h	+++	+
12 h	+++	+
24 h	+++	+
48 h	+	+
4 d	+	+
12 d	+	+
20 d	+	+

How do either macrophages or neutrophils induce vasospasm after entering the subarachnoid space?

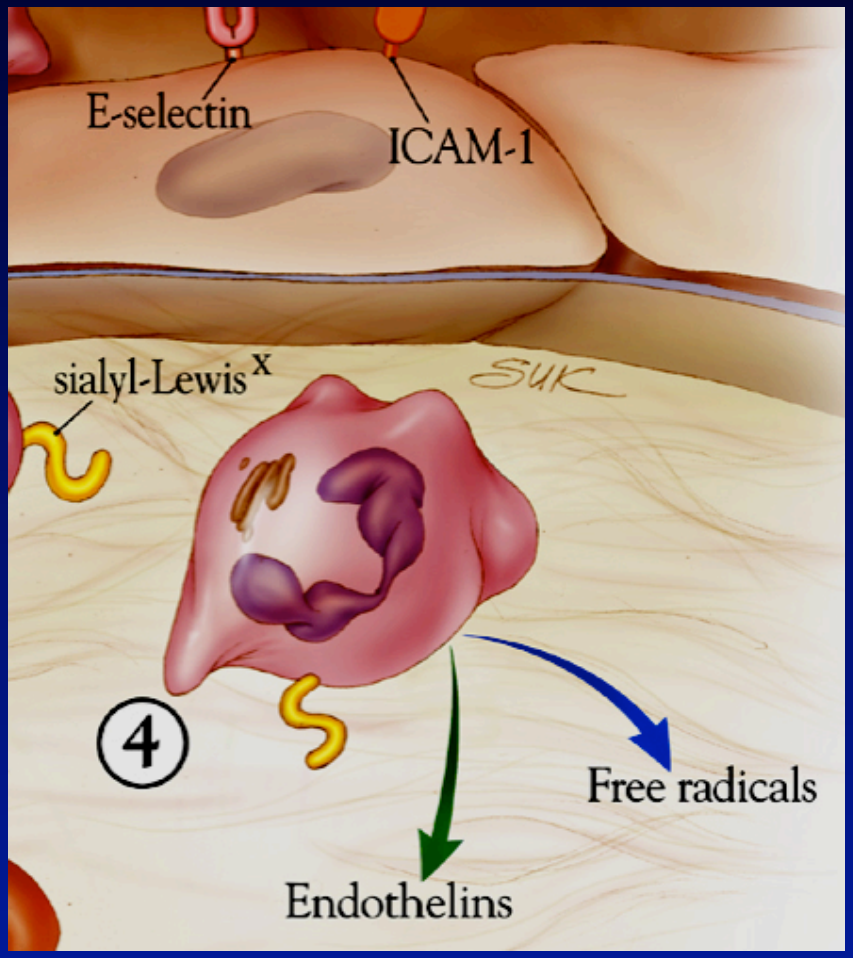
"Endothelins, peptides with potent vasoactive properties, are produced by human macrophages"
Ehrenreich H et al., ***J Exp Med*** 172: 1741, 1990

"Activated neutrophils inhibit cerebrovascular endothelium-dependent relaxations in vitro"
Csaki C et al., ***Life Sci*** 49: 1087, 1991

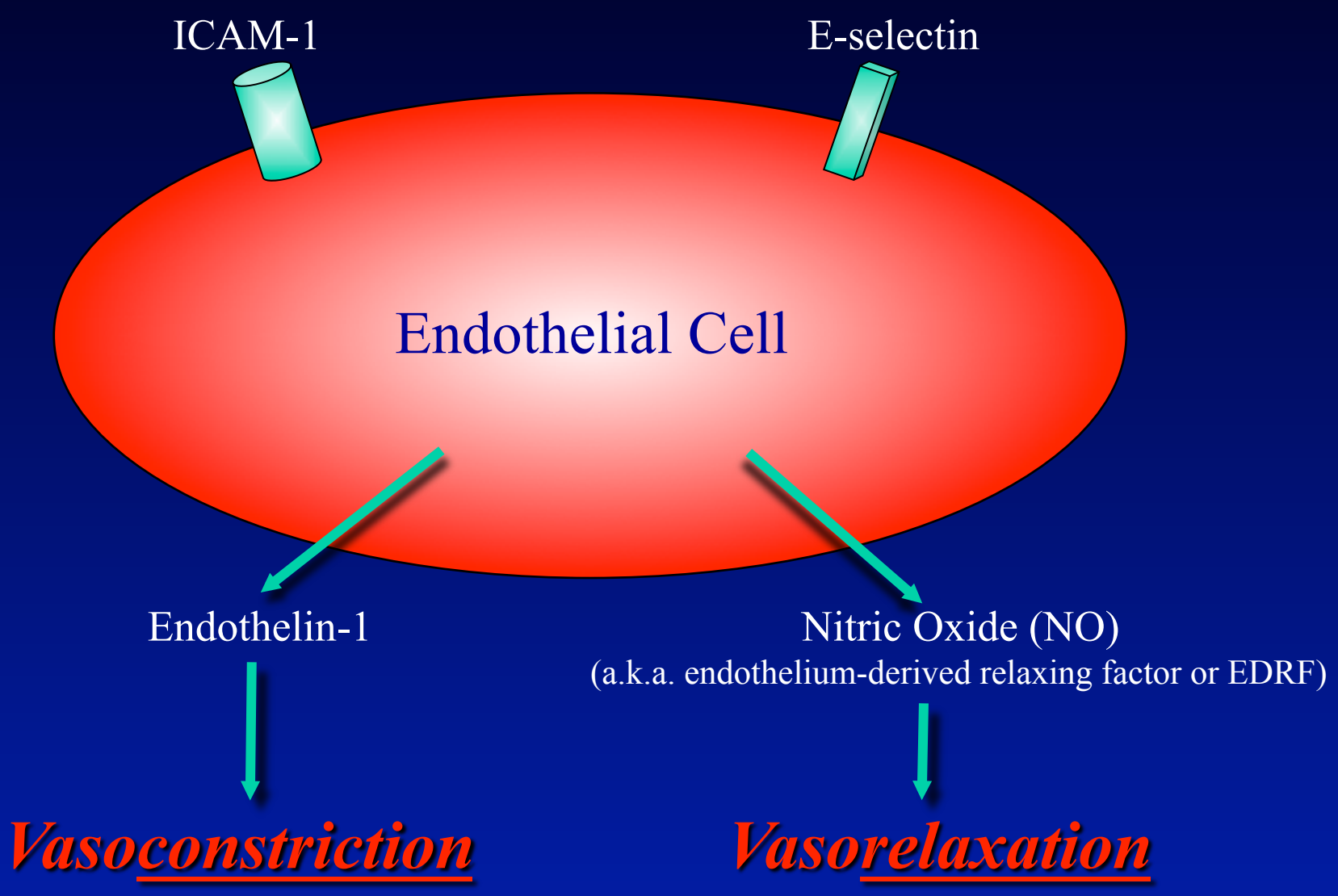
"The endothelium-dependent relaxation of human middle cerebral artery: Effect of activated neutrophils"
Akopov SE et al., ***Experientia*** 48: 34, 1992

"Endothelin-1 in subarachnoid hemorrhage: An acute-phase reactant produced by CSF leukocytes"
Fasbender K et al., ***Stroke*** 31: 2971, 2000

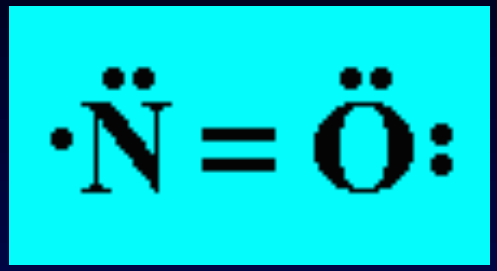
"The biosynthesis of endothelin-1 by human polymorphonuclear leukocytes"
Sessa WC et al., ***Biochem Biophys Res Commun*** 174: 613, 1991



Maintenance of Vascular Tone by Endothelial Cells: Nitric Oxide (NO) and Endothelins



Favorable Properties of Nitric Oxide



1. Vasodilator

2. Anti-inflammatory
   - Inhibits leukocyte-endothelial cell interactions by inhibiting ICAM-1 upregulation

Unfavorable Properties of Nitric Oxide

1. Extremely short half-life (seconds)

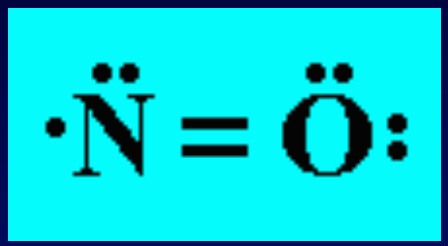
2. Toxic when given systemically (hypotension)

NO is not only a potent vasodilator, but also an inhibitor of ICAM-1 expression

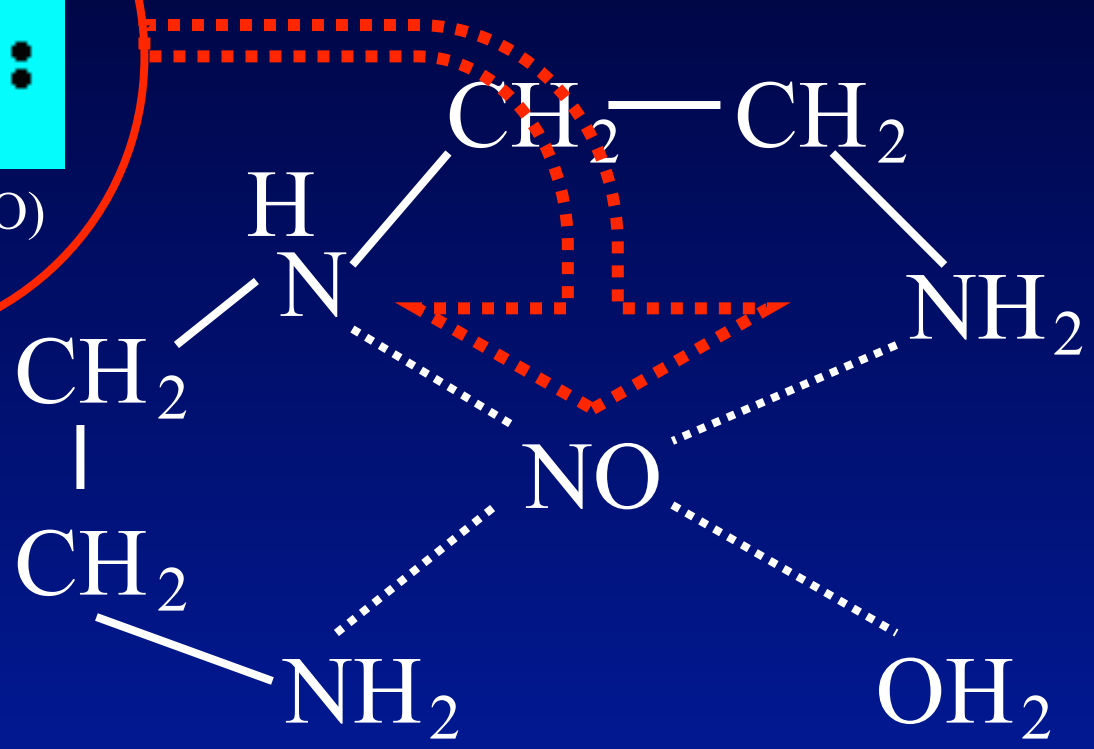
1. D. Berendji-Grun et al. (Dusseldorf, Germany)
   Nitric oxide inhibits endothelial IL-1β-induced ICAM-1 gene expression at the transcriptional level decreasing Sp1 and AP-1 activity
   Molecular Medicine 7: 748-754, 2001

2. A. Marconi et al. (Villejuif and Lyon, France)
   Naftidrofuryl-driven regulation of endothelial ICAM-1 involves nitric oxide.
   Free Radical Biology & Medicine 34: 616-625, 2003

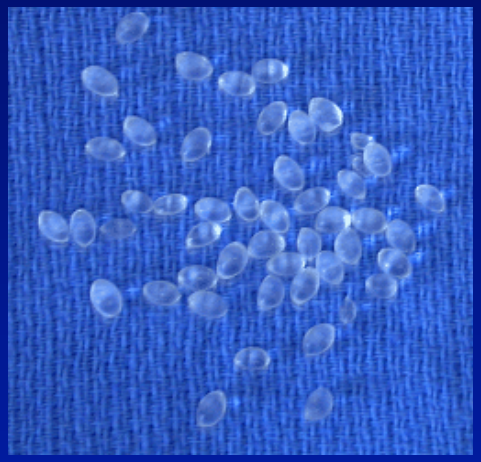
Diethylenetriamine-Nitric Oxide in Ethylene-Vinyl Acetate Copolymer (DETA-NO / EVAc)



Nitric oxide (NO)

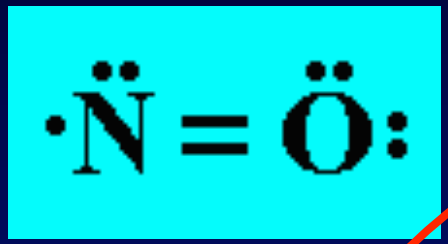


Diethylenetriamine (DETA)

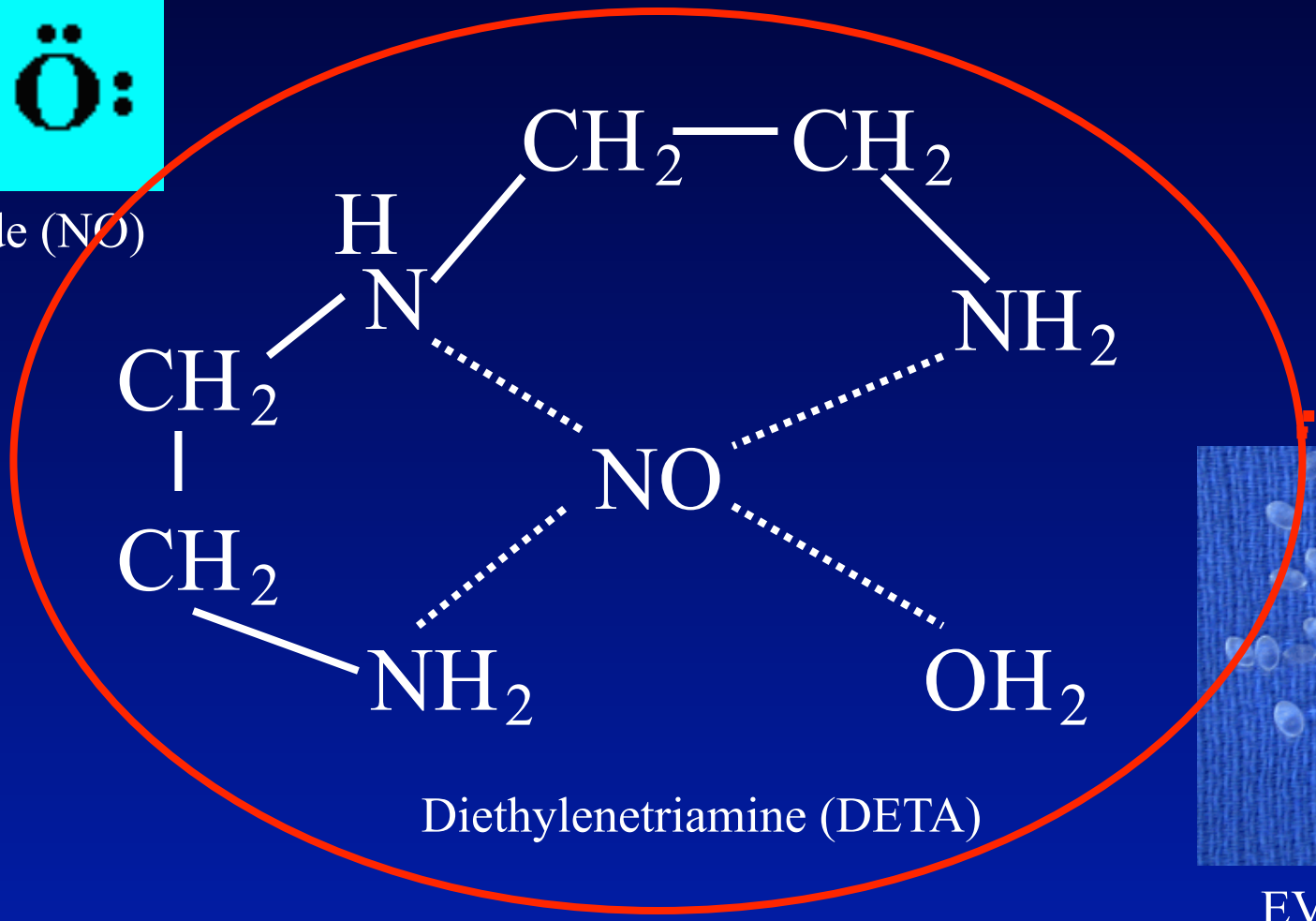


EVAc polymer

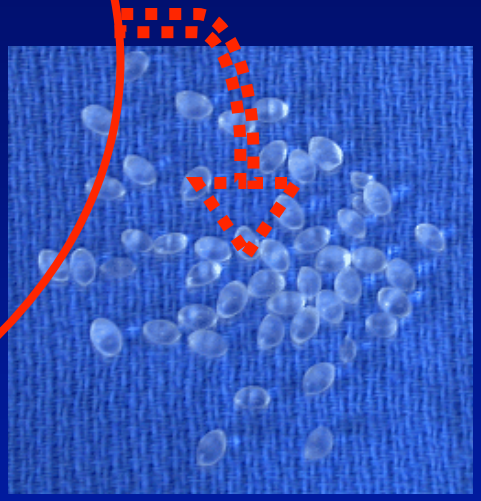
Diethylenetriamine-Nitric Oxide in Ethylene-Vinyl Acetate Copolymer (DETA-NO / EVAc)



Nitric oxide (NO)

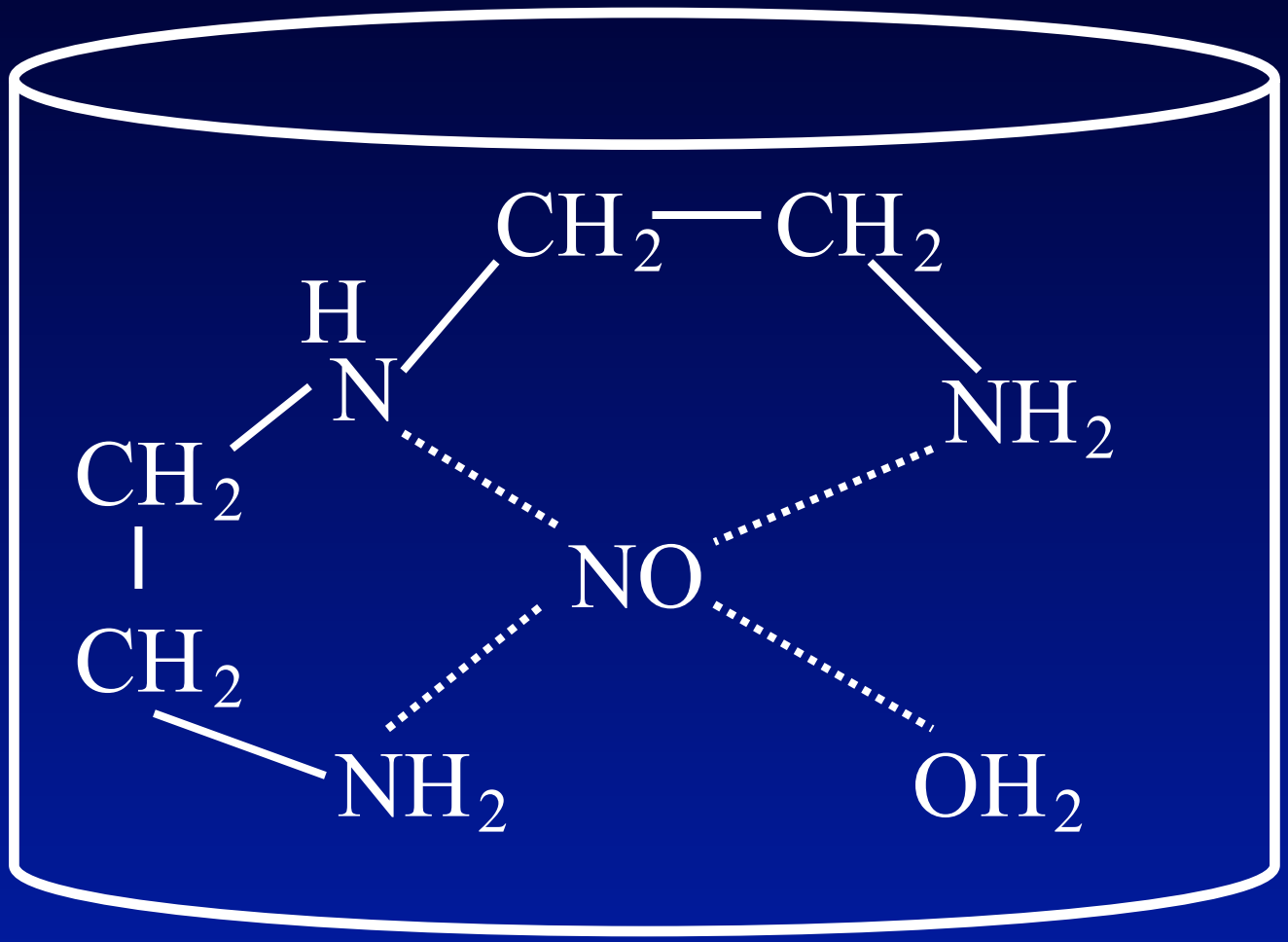


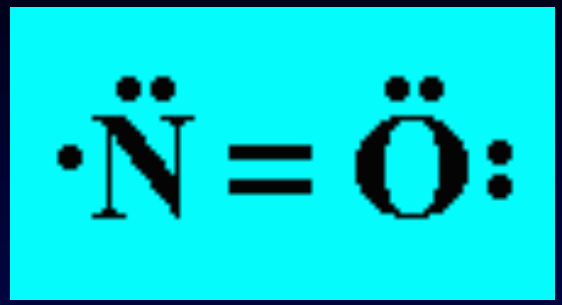
Diethylenetriamine (DETA)

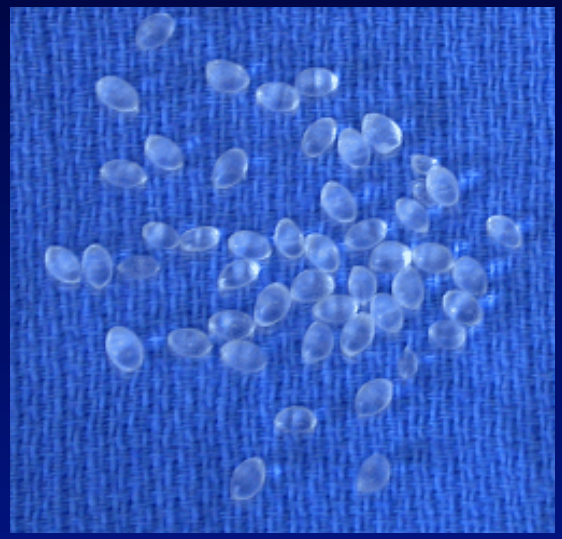


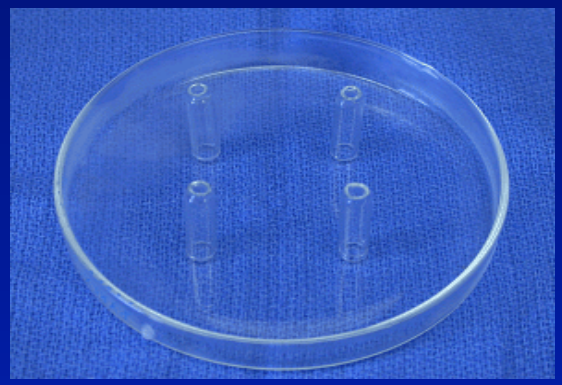
EVAc polymer

DETA-NO in EVAc









Neurosurgery 49: 945-953, October 2001

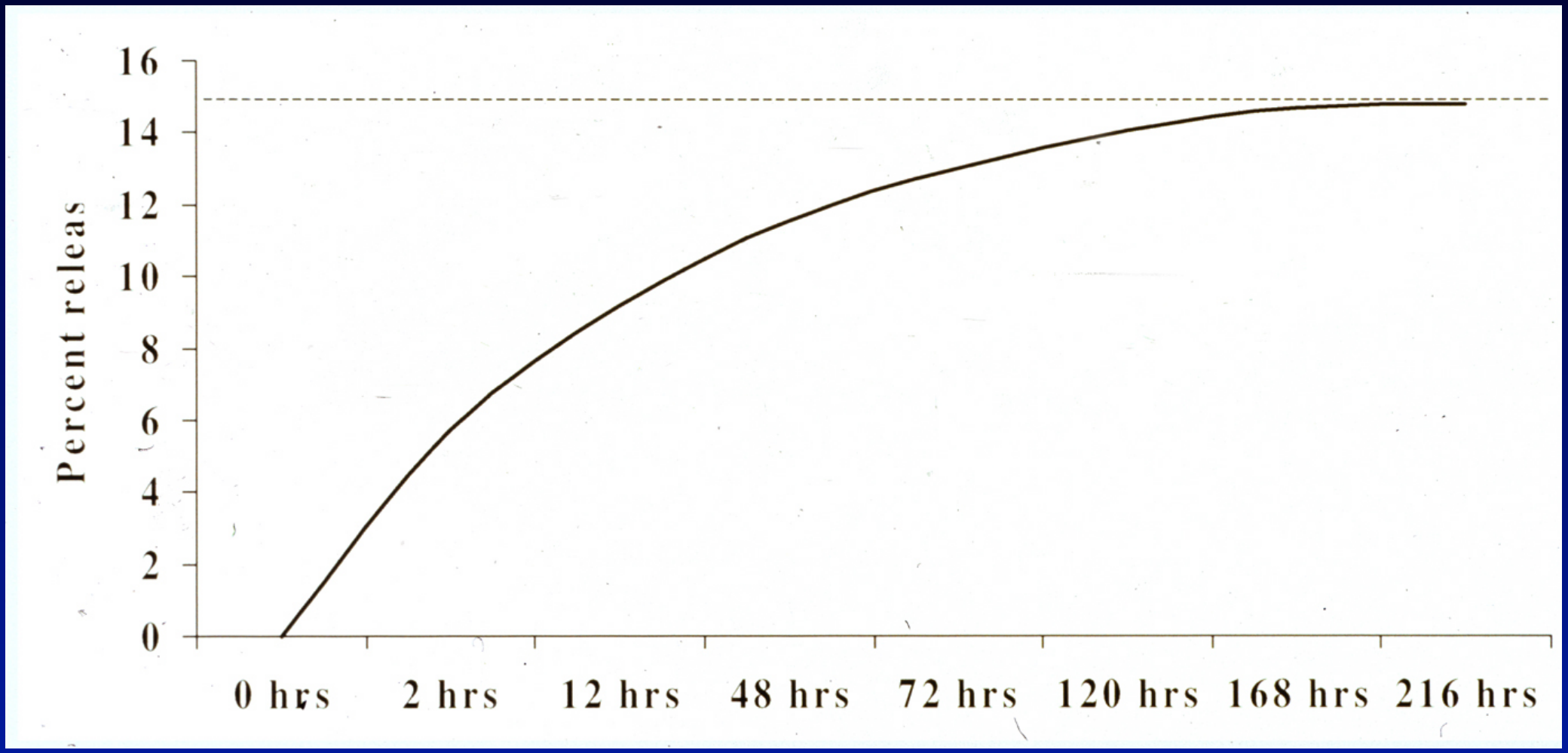
Prevention and Reversal of Experimental Posthemorrhagic Vasospasm by the Periadventitial Administration of Nitric Oxide from a Controlled-release Polymer

Travis S. Tierney, D.Phil.,
Richard E. Clatterbuck, M.D., Ph.D.,
Christopher Lawson, M.D., Quoc-Anh Thai, M.D.,
Laurence D. Rhines, M.D., Rafael J. Tamargo, M.D.

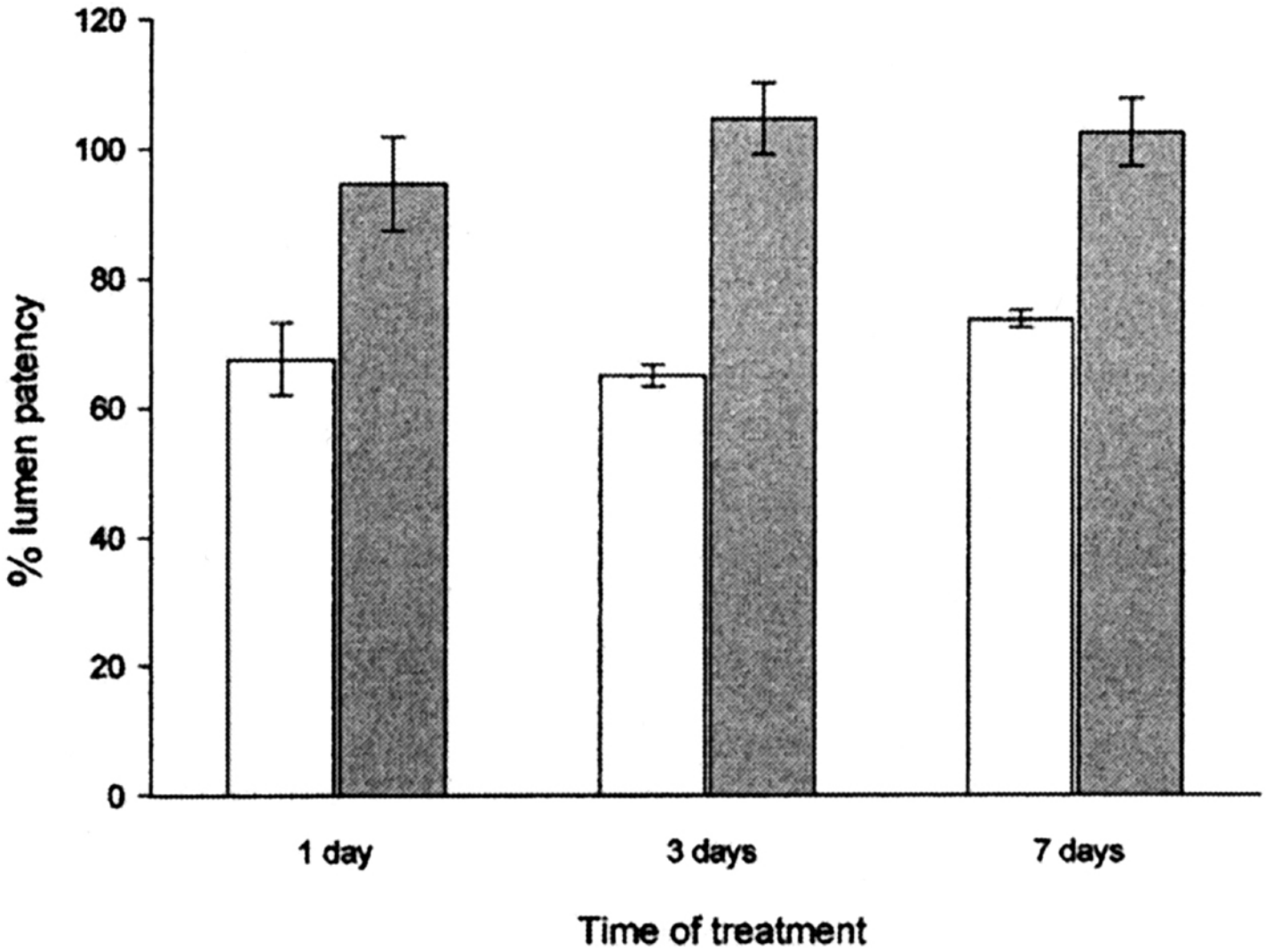
Department of Neurological Surgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland

- Rat femoral artery model
- Diethylenetriamine/nitric oxide (DETA/NO) in EVAc
- Controlled release of DETA/NO in EVAc prevents vasospasm

Controlled Release of DETA/NO from EVAc



DETA/NO in EVAc Prevents Vasospasm in Rats



Stroke 33: 2681-2686, November 2002

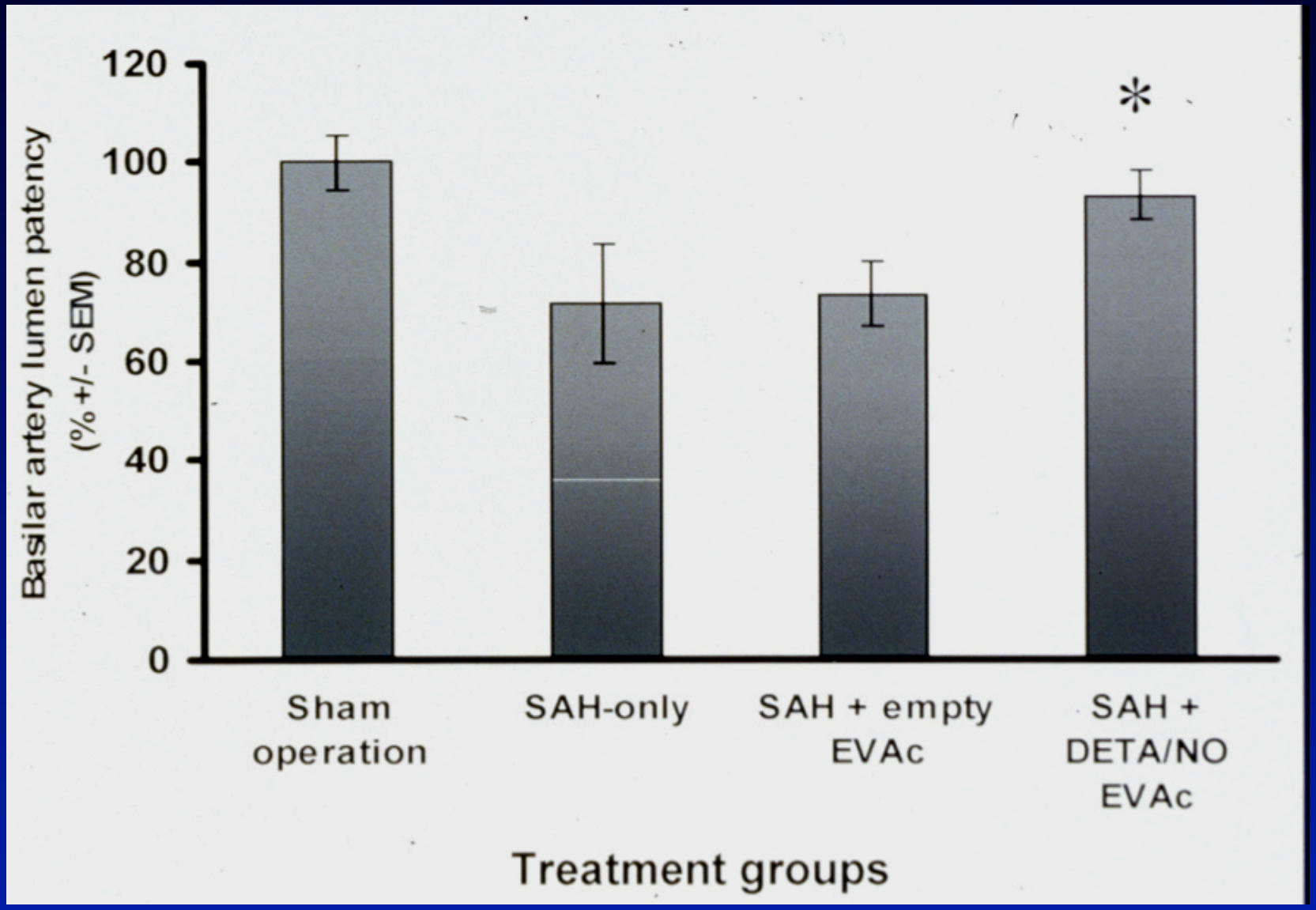
Prevention of Experimental Cerebral Vasospasm by Intracranial Delivery of a Nitric Oxide Donor From a Controlled-Release Polymer

Toxicity and Efficacy Studies in Rabbits and Rats

Patrik Gabikian, MD; Richard E. Clatterbuck, MD, PhD; Charles G. Eberhart, MD, PhD; Betty M. Tyler, BA; Travis S. Tierney, DPhil; Rafael J. Tamargo, MD

- Rabbit SAH model (n=20, 4 experimental groups)
- DETA/NO in EVAc (20%), DETA/NO dose of 0.5 mg/kg
- Animals sacrificed at 72 hr and basilar arteries harvested
- DETA/NO treatment increased lumen patency (93.0 $\pm$ 4.9% vs. 71.4 $\pm$ 11.9%, p=0.035)

DETA/NO in EVAc Prevents Vasospasm in Rabbits



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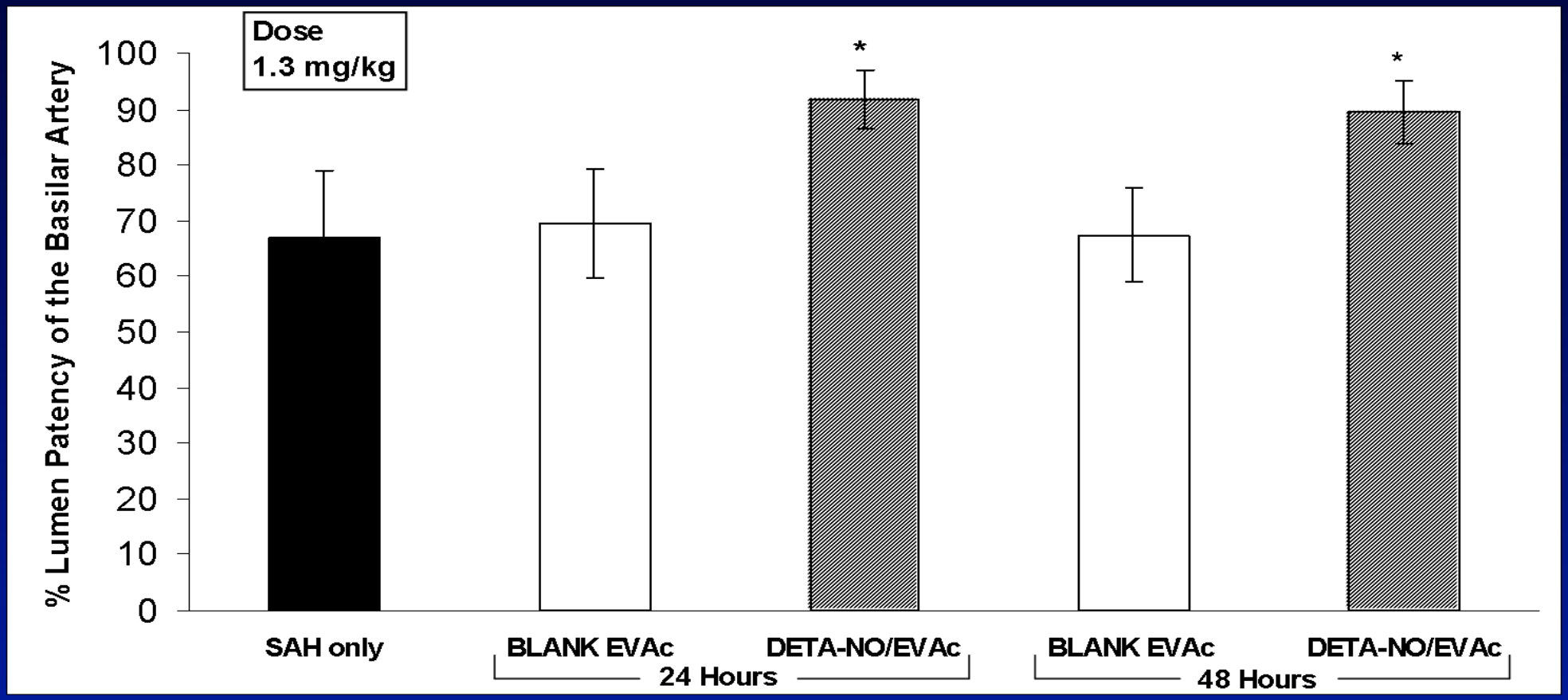
Department of Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, Maryland

Neurosurgery 55: 1393-1400, December 2004

Delayed Intracranial Delivery of a Nitric Oxide Donor from a Controlled-Release Polymer Prevents Experimental Cerebral Vasospasm in Rabbits

- Rabbit SAH model (n=52, 4 groups)
- DETA/NO in EVAc (20%), DETA/NO doses of 0.5 mg/kg or 1.3 mg/kg, at 24 or 48 hr
- Animals sacrificed at 72 hr after SAH and basilar arteries harvested
- DETA/NO treatment (1.3 mg/kg) increased lumen patency at either 24 or 48 hr
  At 24 hr: 97 $\pm$ 6 vs. 73 $\pm$ 10%, p=0.0396
  At 48 hr: 94 $\pm$ 6 vs. 71 $\pm$ 9%, p=0.03

Delayed Treatment with DETA-NO in EVAc Prevents Vasospasm in Rabbits: Dose of 1.3 mg/kg



Journal of Neurosurgery 103: 745-751, October 2005

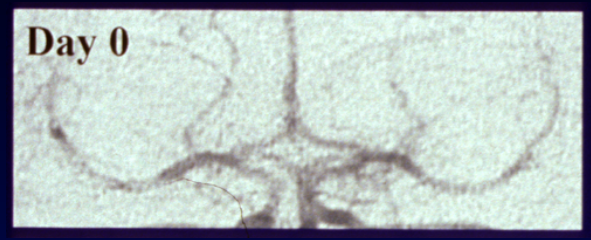
Controlled release of a nitric oxide donor for the prevention of delayed cerebral vasospasm following experimental subarachnoid hemorrhage in nonhuman primates

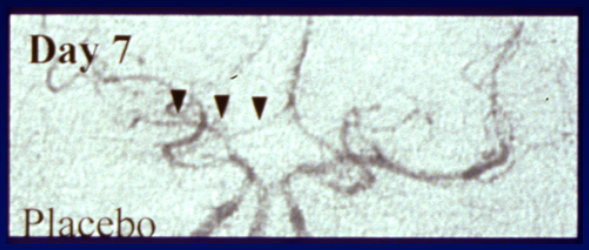
Richard E. Clatterbuck, M.D., Ph.D., Philippe Gailloud, M.D., Travis Tierney, M.D., D.Phil., Victoria M. Clatterbuck, R.T., Kieran J. Murphy, M.D., and Rafael J. Tamargo, M.D.

Department of Neurosurgery and Division of Interventional Neuroradiology, The Johns Hopkins University School of Medicine, Baltimore, Maryland

- Monkeys (n=10)
- Treatment with DETA-NO in EVAc polymers (4.3 mg/kg)
- Angiography repeated on POD 7
- Nitric oxide (NO) prevents vasospasm

Efficacy Study in Monkeys





1 animal in DETA-NO group died prematurely

ICA measurements:

Blank polymer	60.1 ± 4.4 %
DETA-NO	99.3 ± 1.8 %

($p < 0.001$)

MCA (M1) measurements:

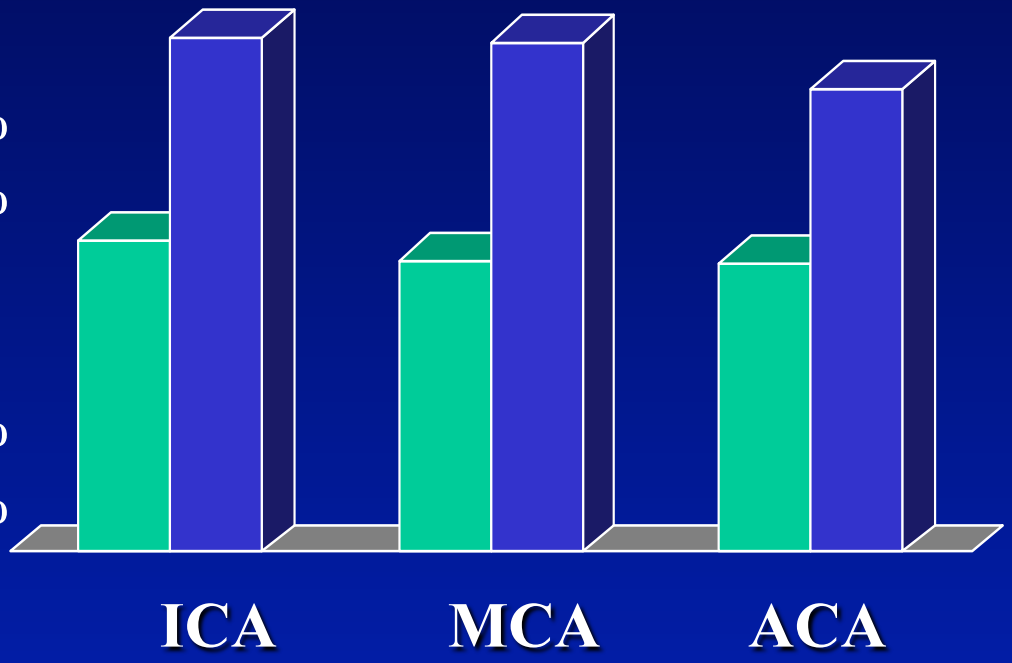
Blank polymer	56.1 ± 3.7 %
DETA-NO	98.4 ± 3.0 %

($p < 0.001$)

ACA (A1) measurements:

Blank polymer	55.8 ± 6.3 %
DETA-NO	89.2 ± 8.5 %

($p < 0.05$)



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Neurosurgery 58: 952-960, May 2006

Intracranial Delivery of the Nitric Oxide Donor Diethylenetriamine/Nitric Oxide from a Controlled-Release Polymer: Toxicity in Cynomolgus Monkeys

13 monkeys, 5 dose groups:

1) 0 mg/kg (n=3)
2) 0.5 mg/kg (n=3)
3) 0.9 mg/kg (n=3)
4) 1.9 mg/kg (n=3) (1 monkey suffered a seizure)
5) 3.2 mg (n=1) (Monkey died 46 hrs post-op)

Toxicity Study in Monkeys

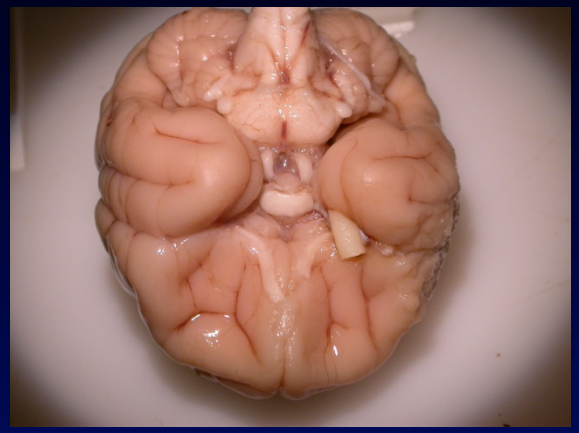
Dose 0 mg/kg (n=3)
No toxicity

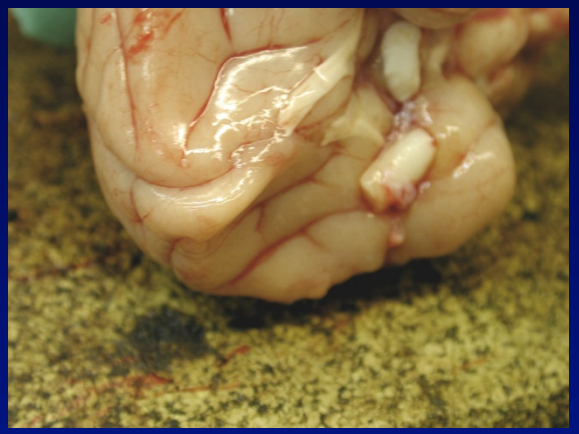
Dose 0.5 mg/kg (n=3)
No toxicity

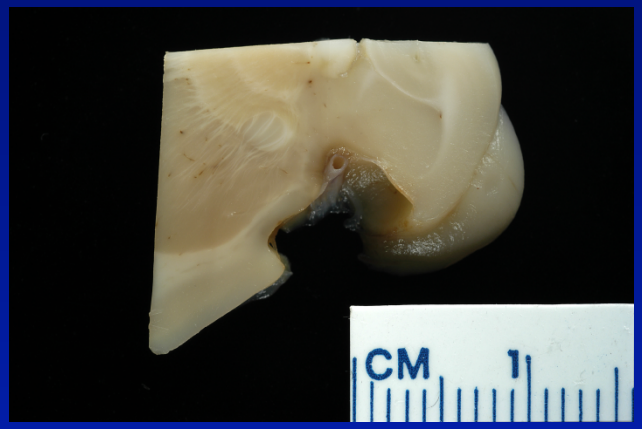
Dose 0.9 mg/kg (n=3)
No toxicity

Dose 1.9 mg/kg (n=3)
1 seizure, full recovery

Dose 3.2 mg/kg (n=1)
Death (focal hemorrhage)





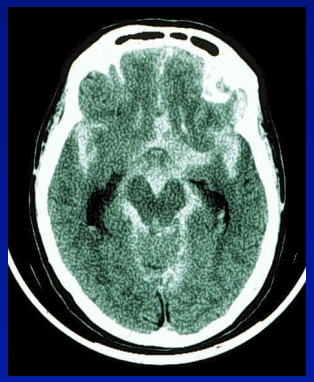


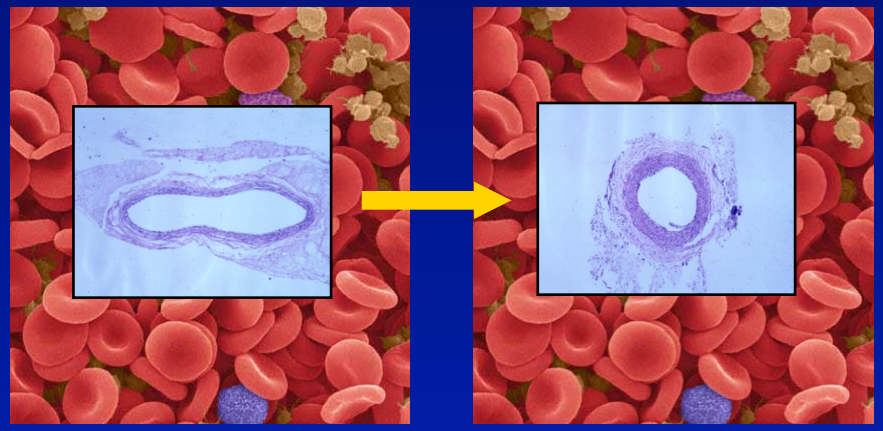
Does the inflammatory hypothesis of vasospasm help predict unexpected results?

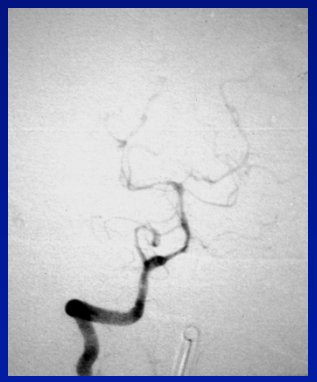
1. In the laboratory, does a purely inflammatory stimulus (like LPS) induce vasospasm in the absence of RBCs in the subarachnoid space?

2. Clinically, does a purely inflammatory disease (like meningitis) induce clinically significant vasospasm in the absence of SAH?

3. Do macrophage-hemoglobin interactions predict which patients are at risk to develop severe, symptomatic vasospasm?







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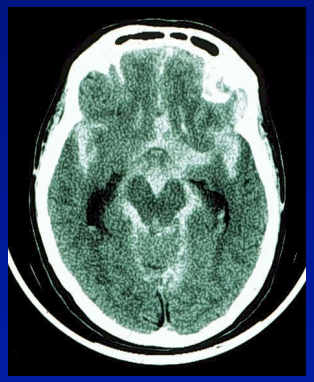
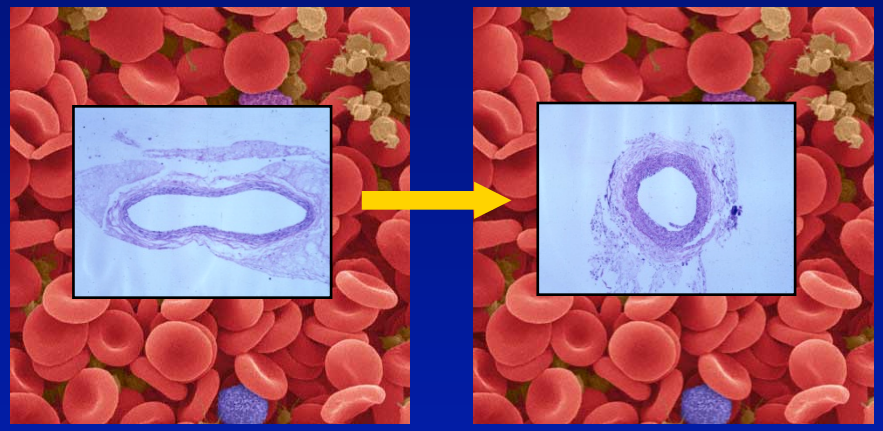
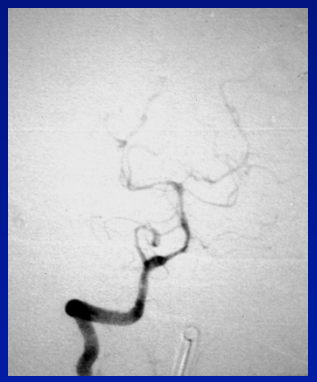






Surgical Neurology 66: 463-469, November 2006

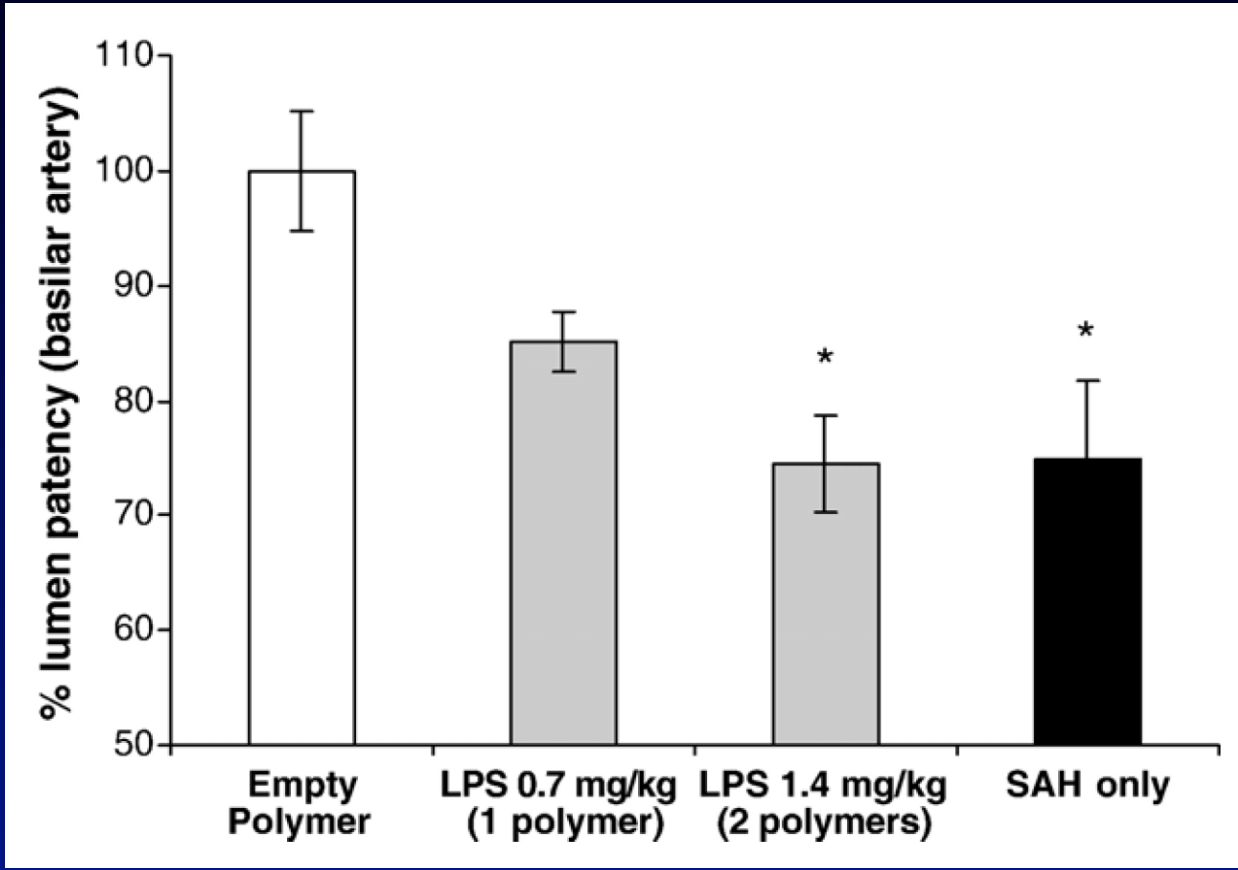
Controlled release of lipopolysaccharide in the subarachnoid space of rabbits induces chronic vasospasm in the absence of blood

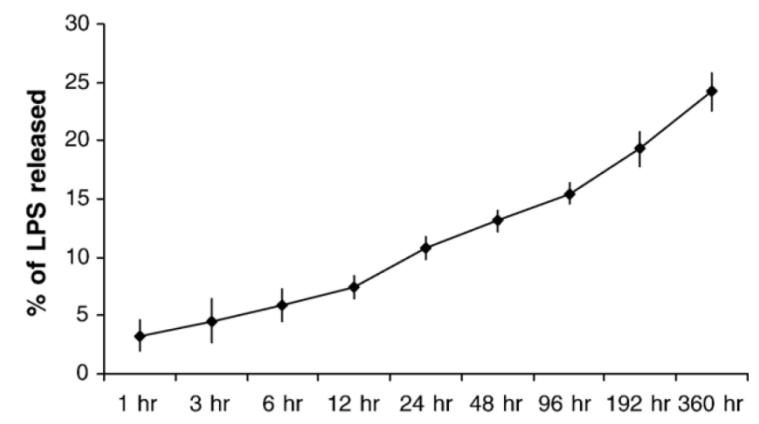
Pablo F. Recinos, BA, Gustavo Pradilla, MD, Quoc-Anh Thai, MD, Marilyn Perez, Alia M. Hdeib, BS, Rafael J. Tamargo, MD, FACS*

Department of Neurosurgery, The Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA

1) Rabbits (n=23) randomized to four groups
2) Lipopolysaccharide (LPS) incorporated
   into ethylene-vinyl acetate (EVAc) polymer
3) LPS/EVAc polymers inserted into cisterna magna:
   - 0.7 mg/kg polymeric LPS dose (actual LPS dose of 33ug/kg per day)
   - 1.4 mg/kg polymeric LPS dose (actual LPS dose of 66 ug/kg per day)
4) One group exposed to SAH
5) Rabbits sacrificed 3 days after SAH and LPS release
6) Basilar artery lumen measured

P.F. Recinos et al. / Surgical Neurology 66 (2006) 463–469





Experimental design

Groups	n	Postoperative deaths	Mean % lumen patency	SEM	*P* (significance <.05)			
					Empty	SAH	LPS 0.7 mg/kg	LPS 1.4 mg/kg
Empty	6	0	100.0	5.2		<.01	NS	<.01
SAH	5	0	74.8	6.9	<.01		NS	NS
LPS 0.7 mg/kg	6	0	85.2	2.6	NS	NS		NS
LPS 1.4 mg/kg	6	2	75.4	4.2	<.01	NS	NS	

Does the inflammatory hypothesis of vasospasm help predict unexpected results?

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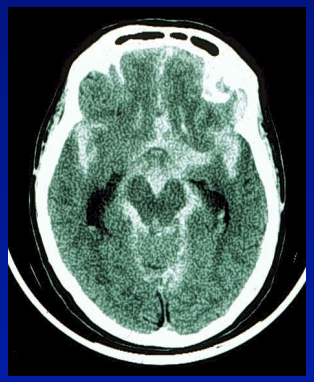

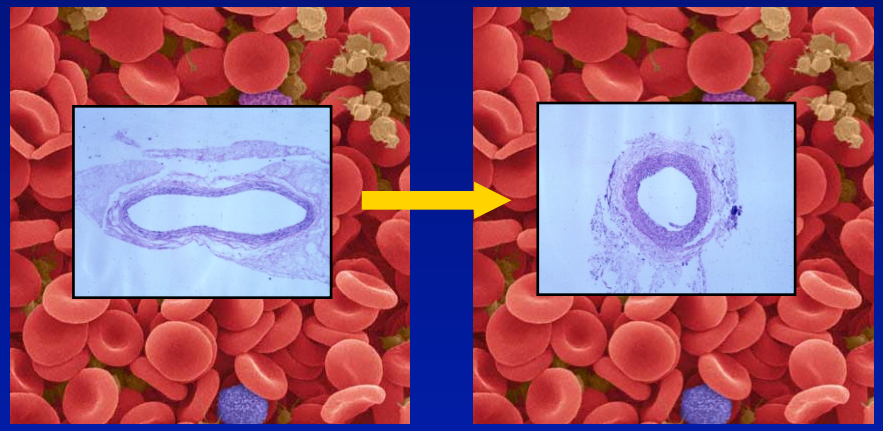

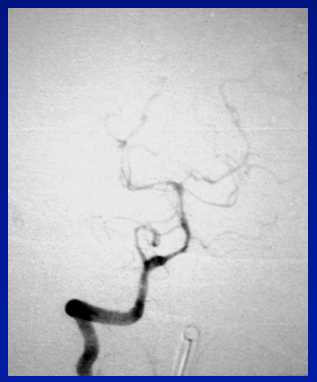

Does the inflammatory hypothesis of vasospasm help predict unexpected results?

1. In the laboratory, does a purely inflammatory stimulus (like LPS) induce vasospasm in the absence of RBCs in the subarachnoid space?

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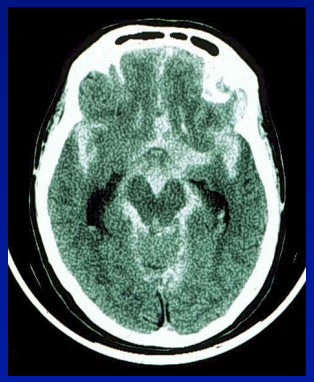

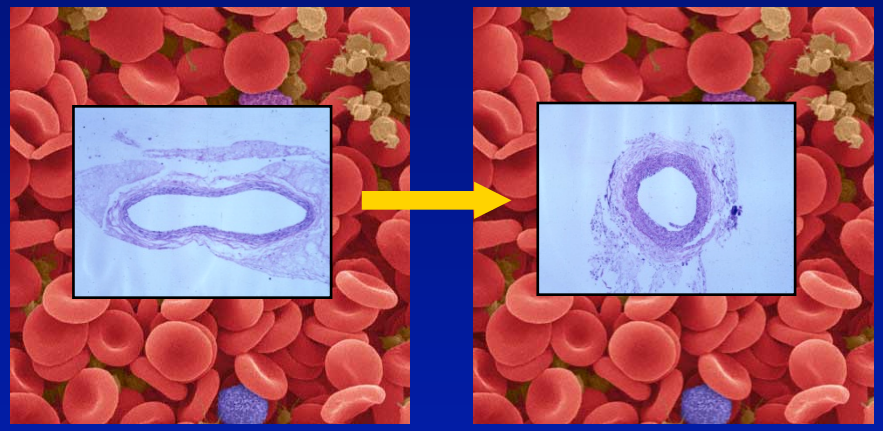

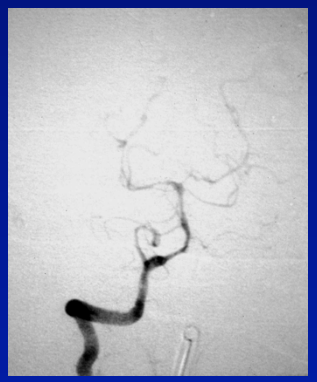

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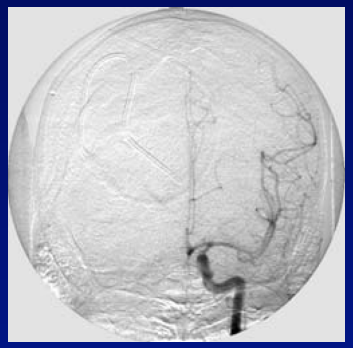
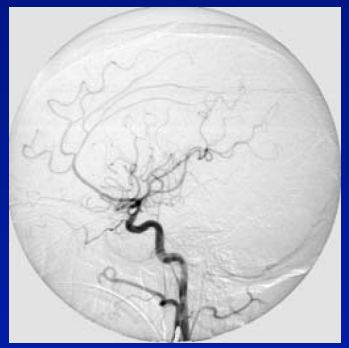
Neurosurgery 60: E206-E207, January 2007

Delayed Cerebral Vasospasm Secondary to Bacterial Meningitis after Lumbosacral Spinal Surgery: Case Report





- 49 y.o. male underwent L2-L4 laminectomy and fusion with instrumentation
- POD 5: Febrile, disoriented
  - CT : Hydrocephalus from meningitis/ventriculitis
  - C1-2 puncture: Gram + cocci, WBC 21,200 (88% PMNs)
  - Started on vancomycin, cefepime, rifampin
  - IVC placed
- POD 6: Wound drainage and lavage
- POD 7-13: Clinical and lab improvement
- POD 14: Expressive aphasia (9 days after Dx of meningitis)
  - MRI negative for CVA, AG and TCDs diagnostic of vasospasm
- POD 15: Triple H therapy started with clinical improvement
- POD >16: Triple H therapy tapered, IVC removed
- POD 30: Discharge to rehabilitation facility
- At 4 months: VPS
- Follow-up at one year

Does the inflammatory hypothesis of vasospasm help predict unexpected results?

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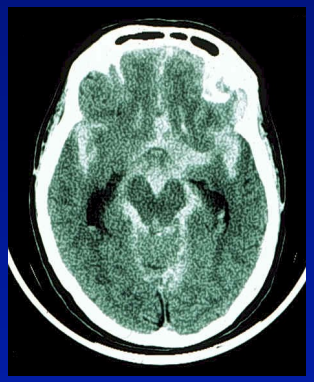

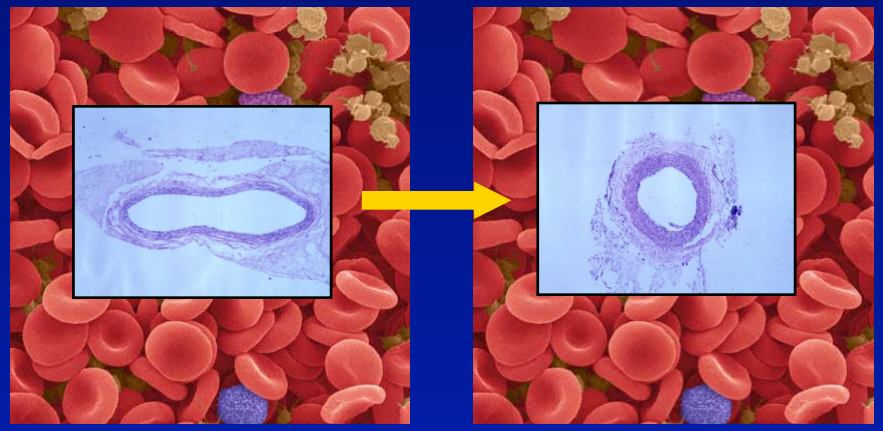

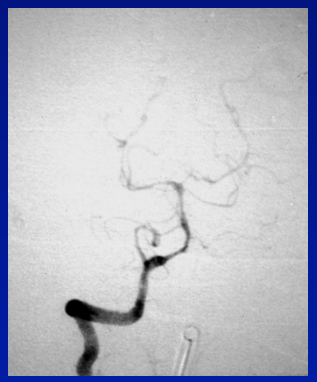

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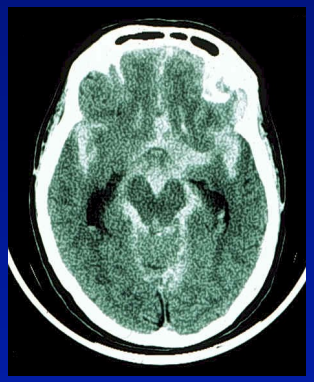
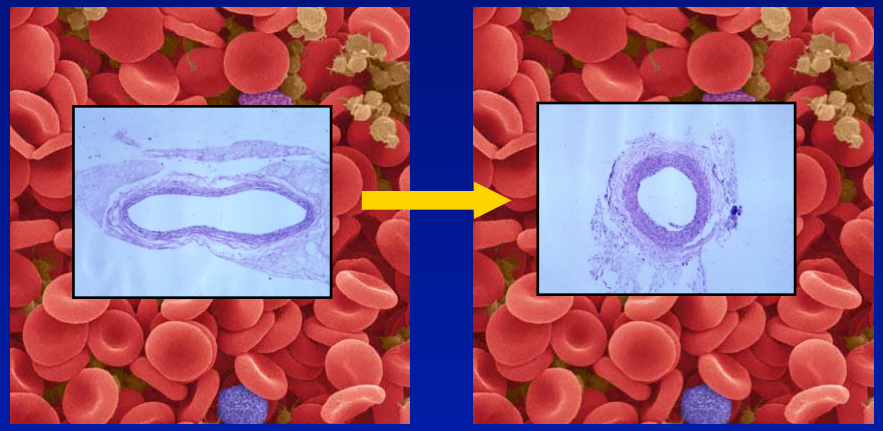
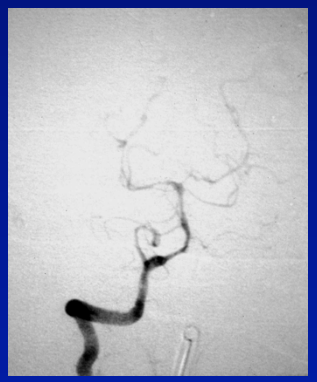
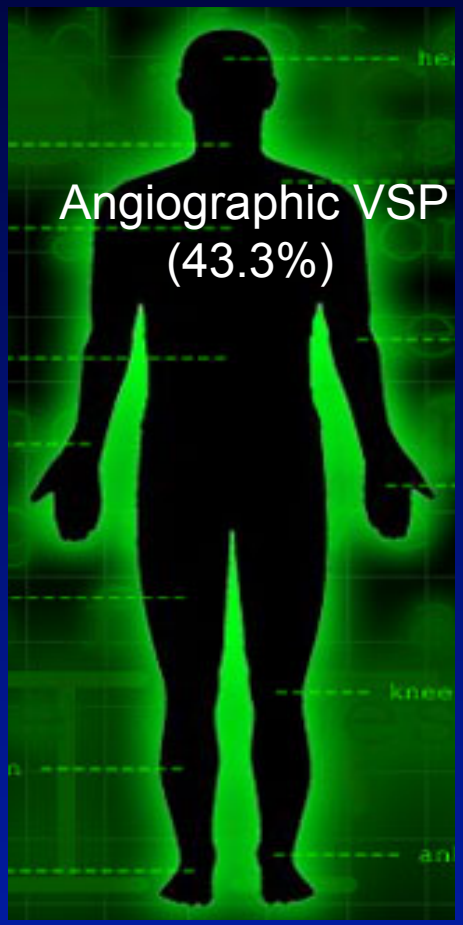




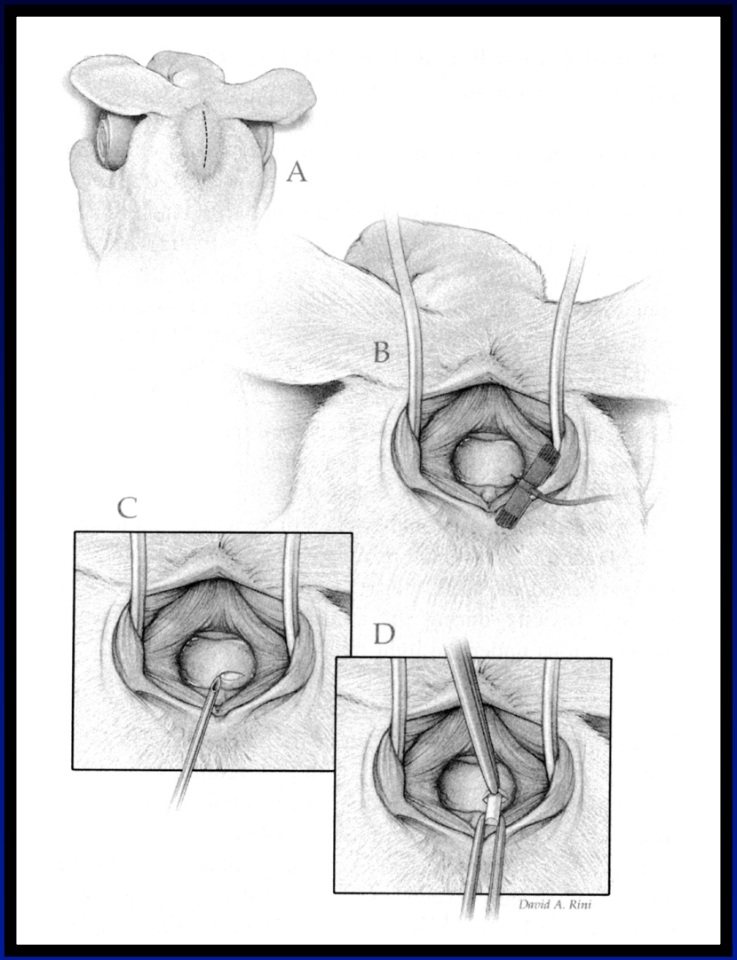


Why do some patients develop symptomatic vasospasm, others only angiographic (asymptomatic) vasospasm, and others no vasospasm at all?

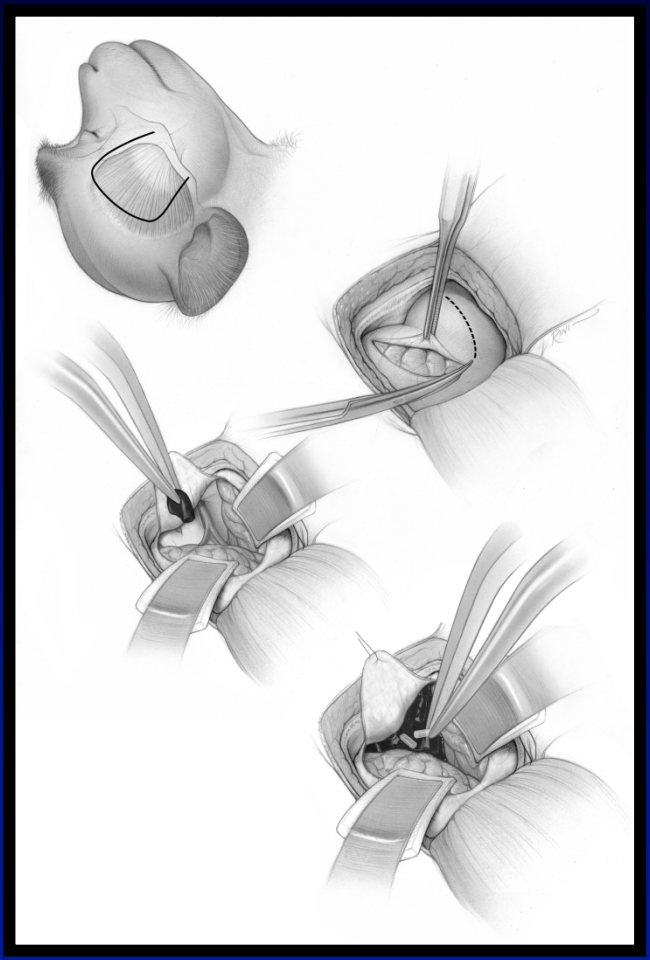


Dorsch, *Br J Neurosurg,* 9: 403, 1995

Why do none of the animal models of SAH and vasospasm results in impaired behavior, ischemic stroke, or death?



Rabbits



Monkeys

Haptoglobin 2-2 Genotype Determines Chronic Vasospasm After Experimental Subarachnoid Hemorrhage

Kaisorn L. Chaichana, BS; Andrew P. Levy, MD, PhD; Rachel Miller-Lotan, PhD; Sophia Shakur, BS; Rafael J. Tamargo, MD, FACS

Background and Purpose—Chronic cerebral arterial vasospasm is the leading cause of morbidity and mortality after aneurysmal subarachnoid hemorrhage (SAH). Not all cases of SAH, however, develop chronic vasospasm. Inflammation, specifically leukocyte–endothelial cell interactions, appears to be critical in vasospasm development. Haptoglobin (Hp) is a serum protein that limits the extent of inflammation after a hemorrhagic event. An individual's Hp genotype may predict the severity of the inflammatory response during a hemorrhagic event, and consequently modulate the risk for vasospasm.

Methods—Sixty mice (Hp 1-1, n=30; Hp 2-2, n=30) underwent injection of either autologous blood or normal saline solution into the cisterna magna. An additional 30 mice (15 per genotype) served as controls. The extent and manifestations of vasospasm were assessed by measuring lumen patency, quantifying activity levels, and counting the number of vessel-infiltrated macrophages/neutrophils at 24 hours after injection, which corresponds to the time of peak vasospasm in mice.

Results—Genetically modified Hp 2-2 mice with SAH had significantly lower basilar artery lumen patencies (mean±SEM; 52.9±1.9% vs 82.3±1.3%; $P<0.01$), reduced activity levels (0.8±0.3 vs 2.4±0.2; $P<0.01$), and increased macrophage/neutrophil counts in the subarachnoid space (31.2±6.3 vs 8.8±1.7, $P<0.01$) as compared with wild-type Hp 1-1 mice.

Conclusions—These findings suggest that the Hp 2-2 genotype is critical for the development of severe vasospasm, which typically occurs 24 hours after SAH in mice. (***Stroke*. 2007;38:3266-3271.**)

Key Words: haptoglobin ■ subarachnoid hemorrhage ■ vasospasm

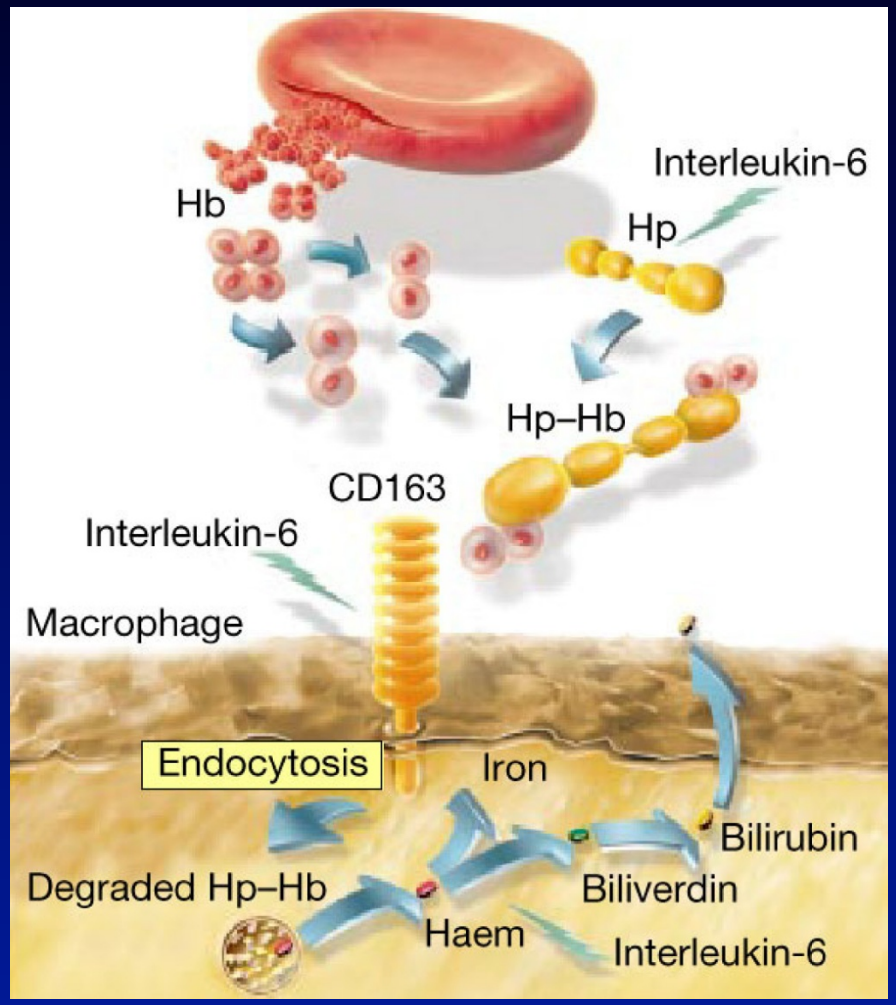
Role of Haptoglobin (Hp) in Hemoglobin (Hgb) Metabolism

1. Extracorpuscular Hgb is toxic

2. **Haptoglobin** is:
   - a serum protein made up of two alpha and two beta chains connected by disulfide bridges
   - produced mostly by hepatocytes

3. Haptoglobin binds free Hgb and presents it to macrophages for phagocytosis (CD163 receptor)

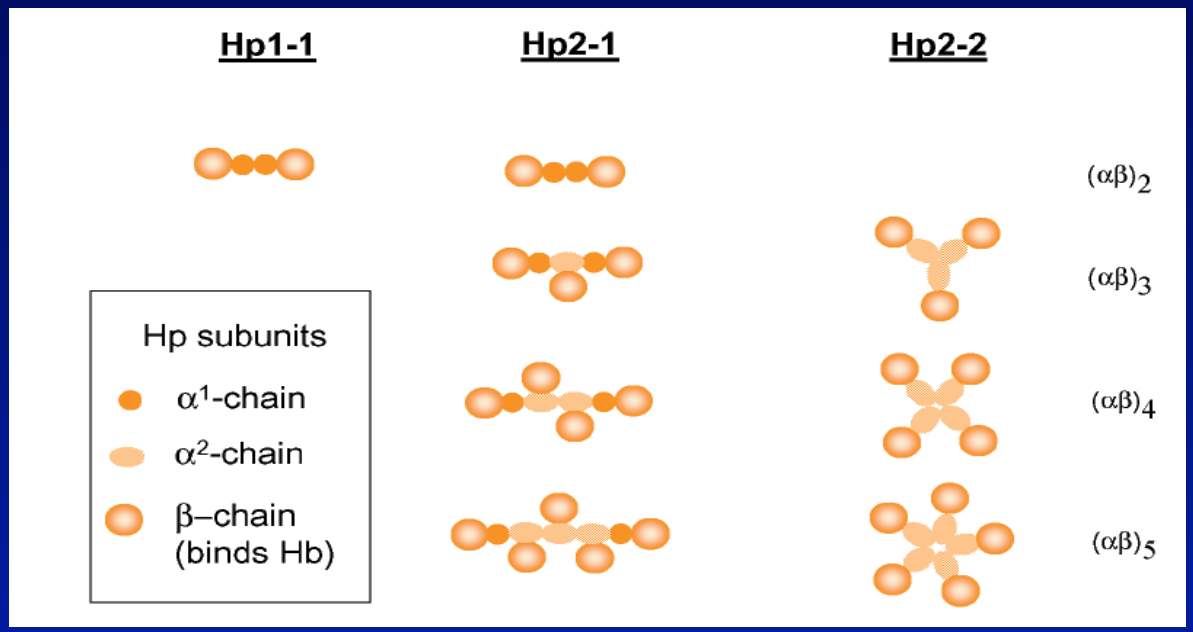
4. Haptoglobin reduces inflammation caused by free Hgb by facilitating macrophage phagocytosis



Dennis C. Nature 409: 141, 2001

Humans are the only species with two alleles for the haptoglobin gene (Hp 1 and Hp 2)

- All species with Hp other than humans are Hp 1-1
- Hp 2 evolved in humans about 100,000 years ago
- Hp 1-1 (linear dimer) more effectively suppresses inflammation
- Hp 2-2 (cyclical polymer) more effectively attenuates infections (Streptococcus pyogenes, Plasmodium falciparum/vivax)



Moestrup et al. *Ann Med* 36: 347, 2004

Comparison of the incidence of vasospasm and the prevalence of haptoglobin (Hp) genotypes

Incidence of Vasospasm	
Symptomatic, angiographic	32.6%
Angiographic only	43.3%
No vasospasm	24.1%

Hp Genotype Distribution	
Hp 2-2	37.4%
Hp 2-1	48.2%
Hp 1-1	14.4%

Dorsch NWC. "Cerebral arterial spasm – a clinical review." Br Jl Nus 9: 403, 1995

Langlois MR, Delanghe JR. "Biological and clinical significance of haptoglobin polymorphism in humans." Clinical Chemistry 42: 1589, 1996.

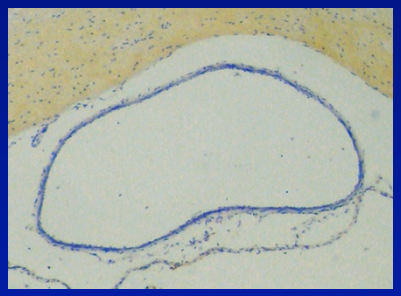
Vasospasm and Hp 2-2 genotype: Experimental design

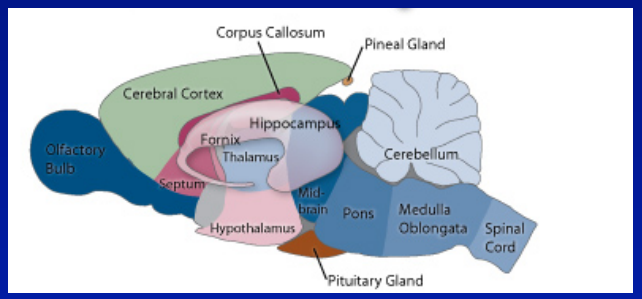
1. Wild-type Hp 1-1 C57Bl/6J mice (n=45) and genetically-modified Hp 2-2 C57Bl/6J mice (Technion Institute, Haifa, Israel) (n=45)

2. Injection of autologous blood or saline into the cisterna magna

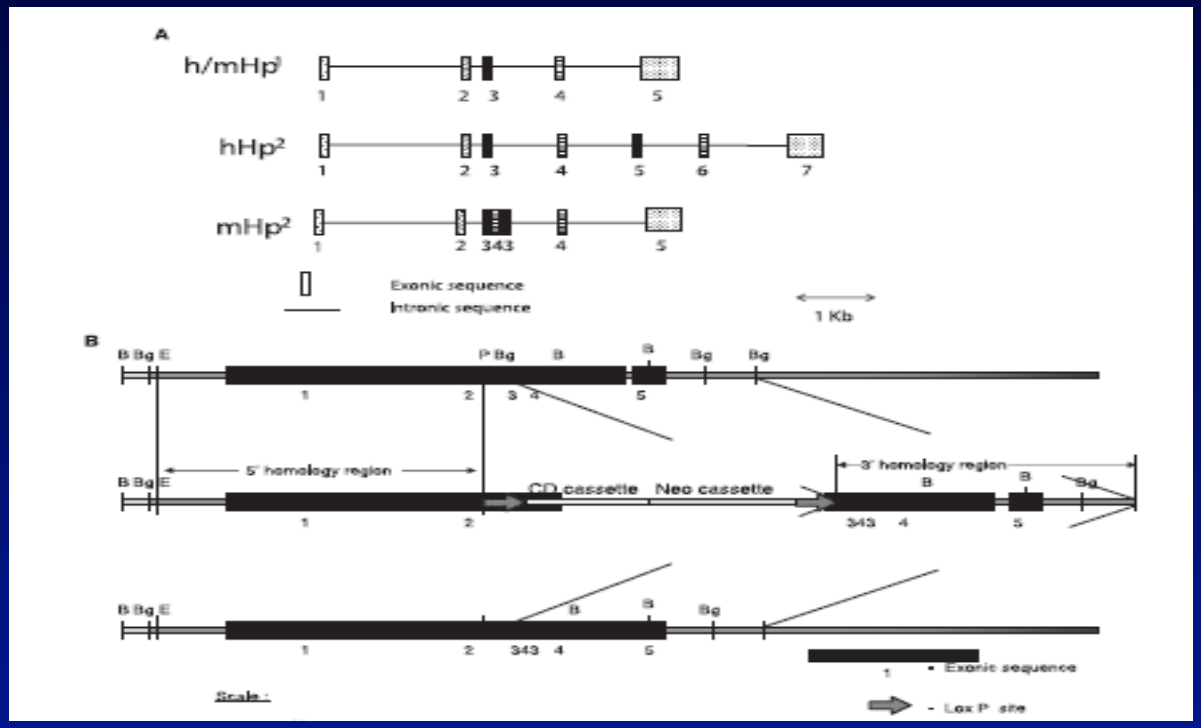
3. Animals were sacrificed at 24 hrs:
   A. Basilar lumen patency
   B. Macrophage/neutrophil concentrations in subarachnoid space
   C. Activity levels (3-point scale)

4. Analysis by Kruskal-Wallis and Student-Newman-Keuls ANOVA





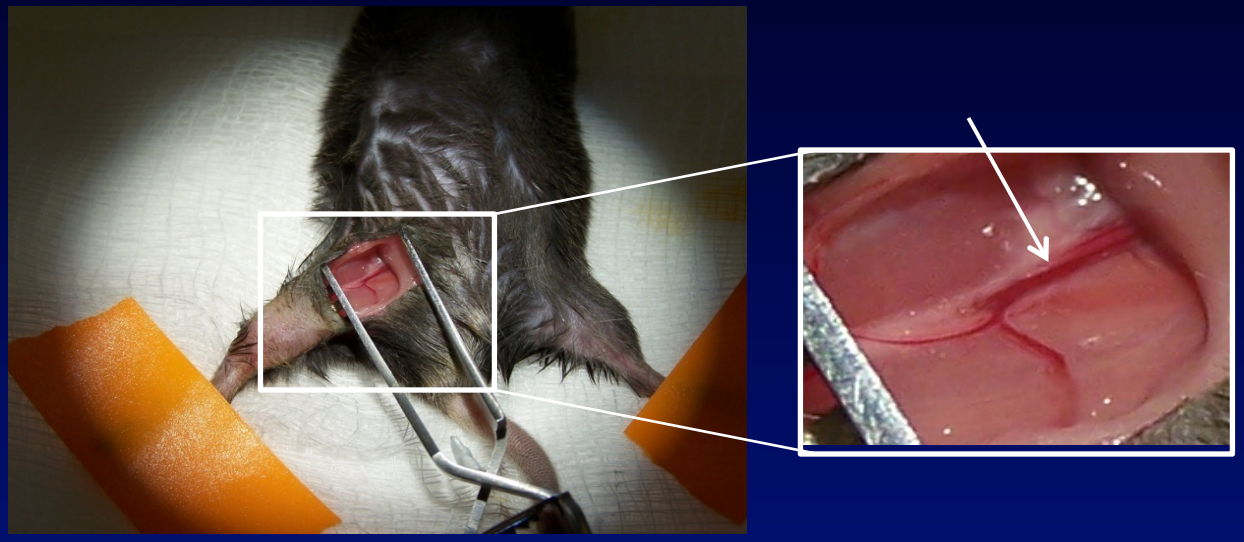
Construction of the Hp 2-2 mouse



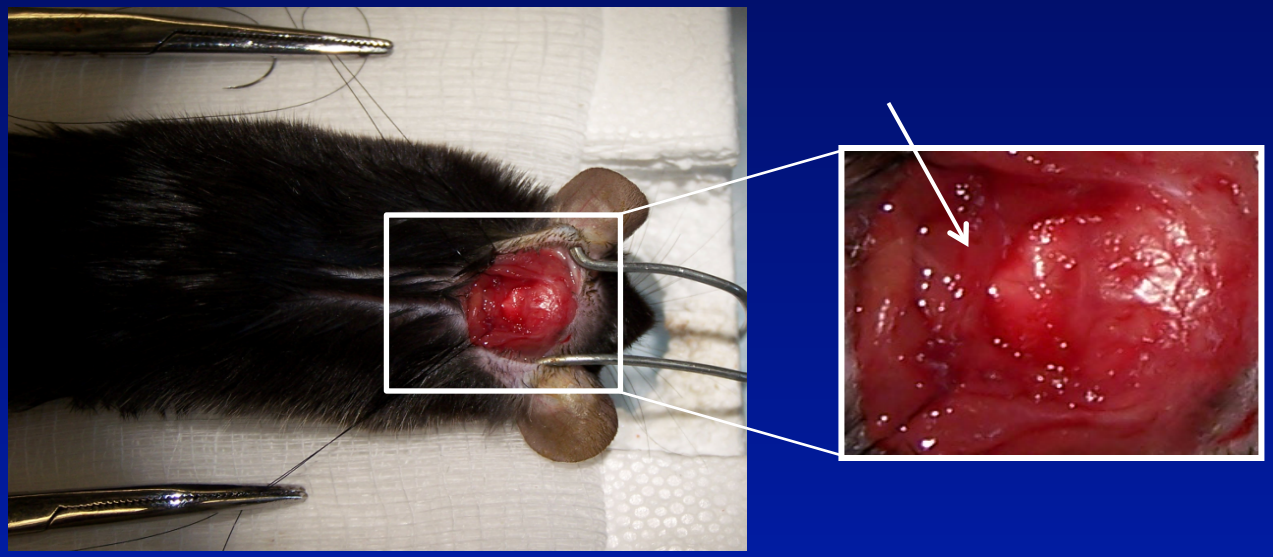
Levy AP et al., *Arterioscler Thromb Vasc Biol,* 27: 134, 2007

- Intragenic duplication of exons 3 and 4
- Hp serum concentration similar in Hp 1-1 and Hp 2-2 mice
- Hp serum levels similar to human levels
- Murine Hp 1-1 and Hp 2-2 are similar in shape, size, and amino acid sequence to human Hp 1-1 and Hp 2-2

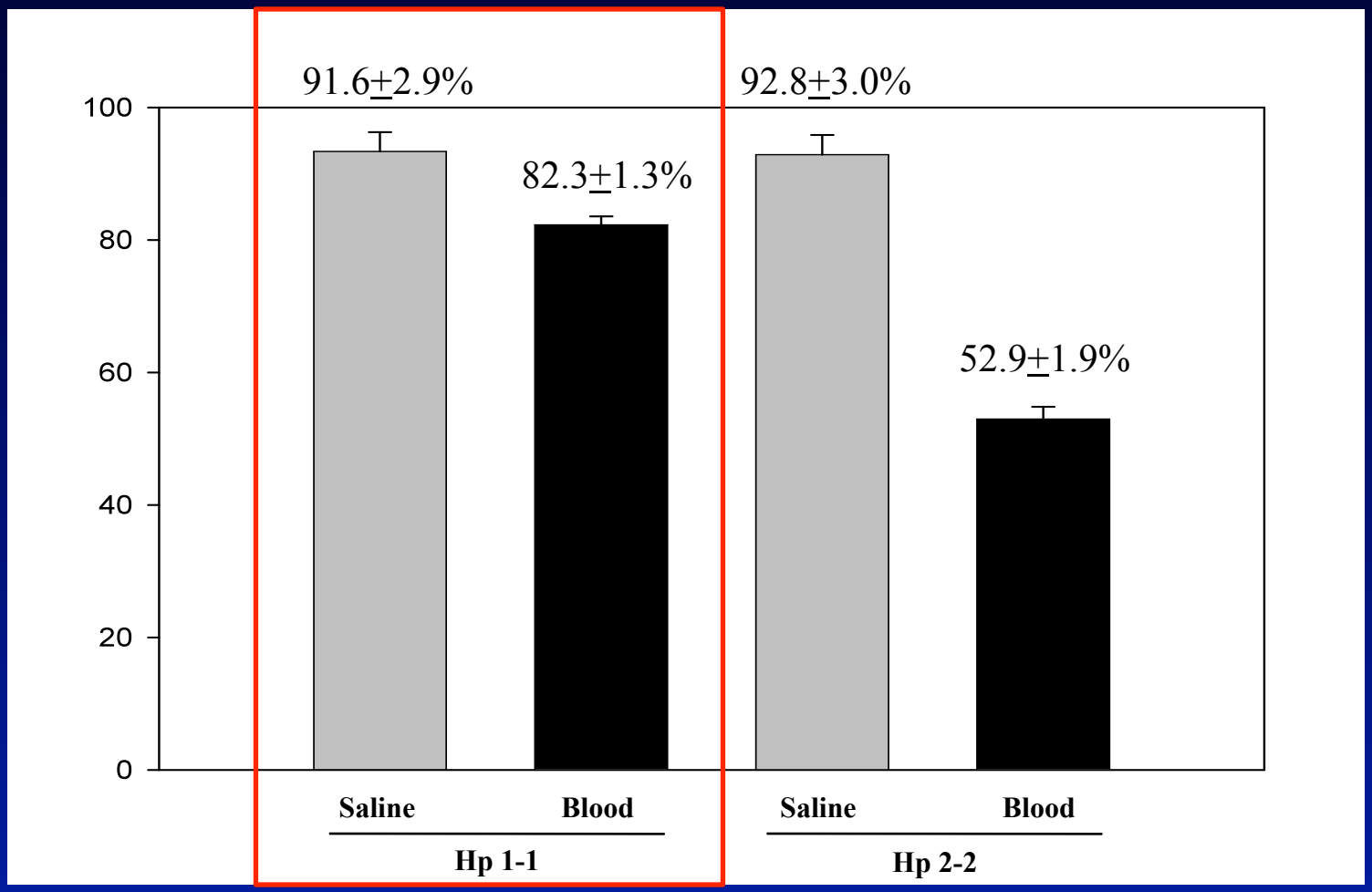
Induction of SAH into Cisterna Magna



1) Autologous blood (60µl) is obtained from the femoral artery
2) Cisterna magna is exposed
3) Blood (60µl) is injected into cisterna magna



Results: Lumen Patency Analysis



p=0.01

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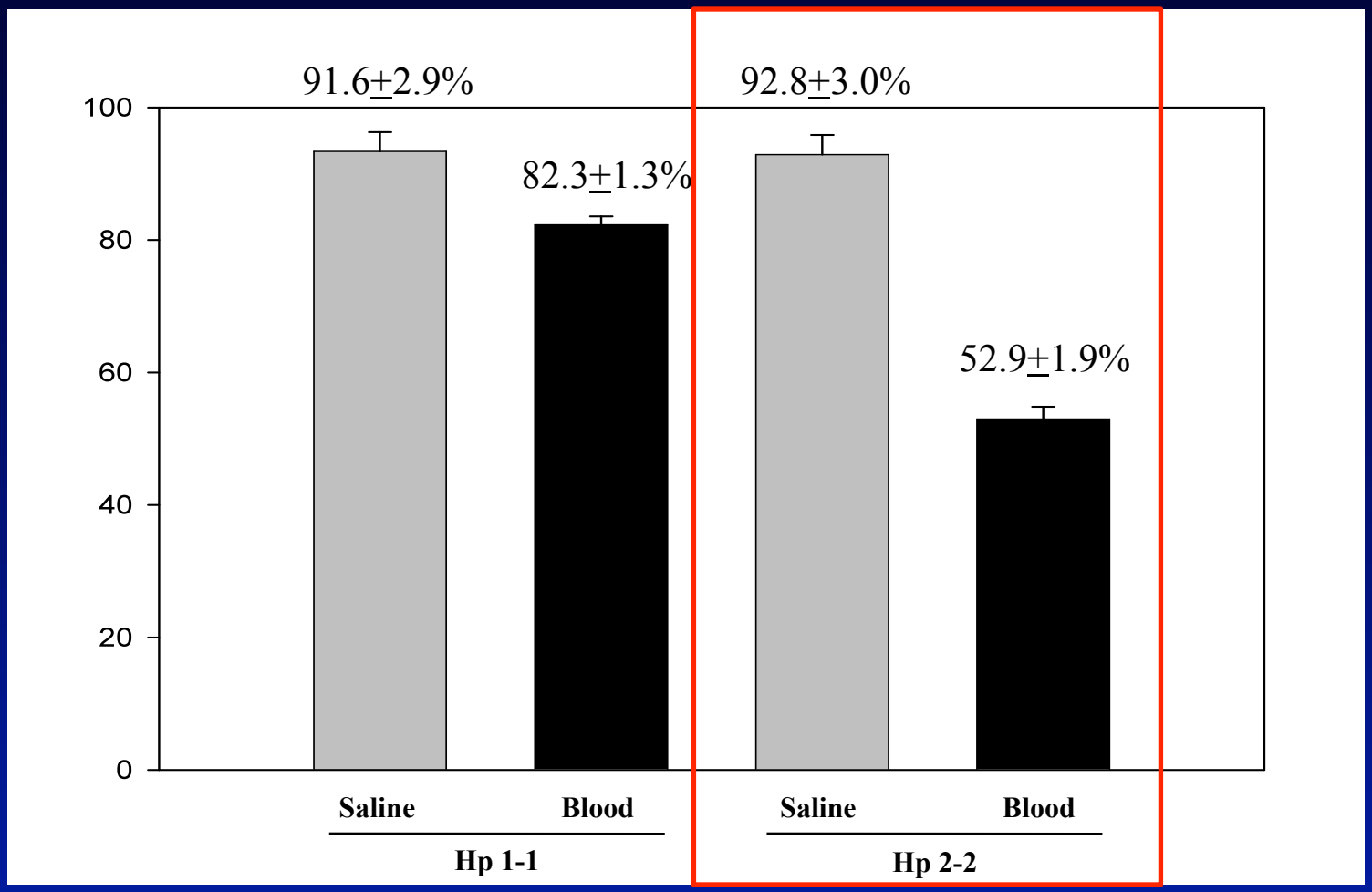

$p<0.001$

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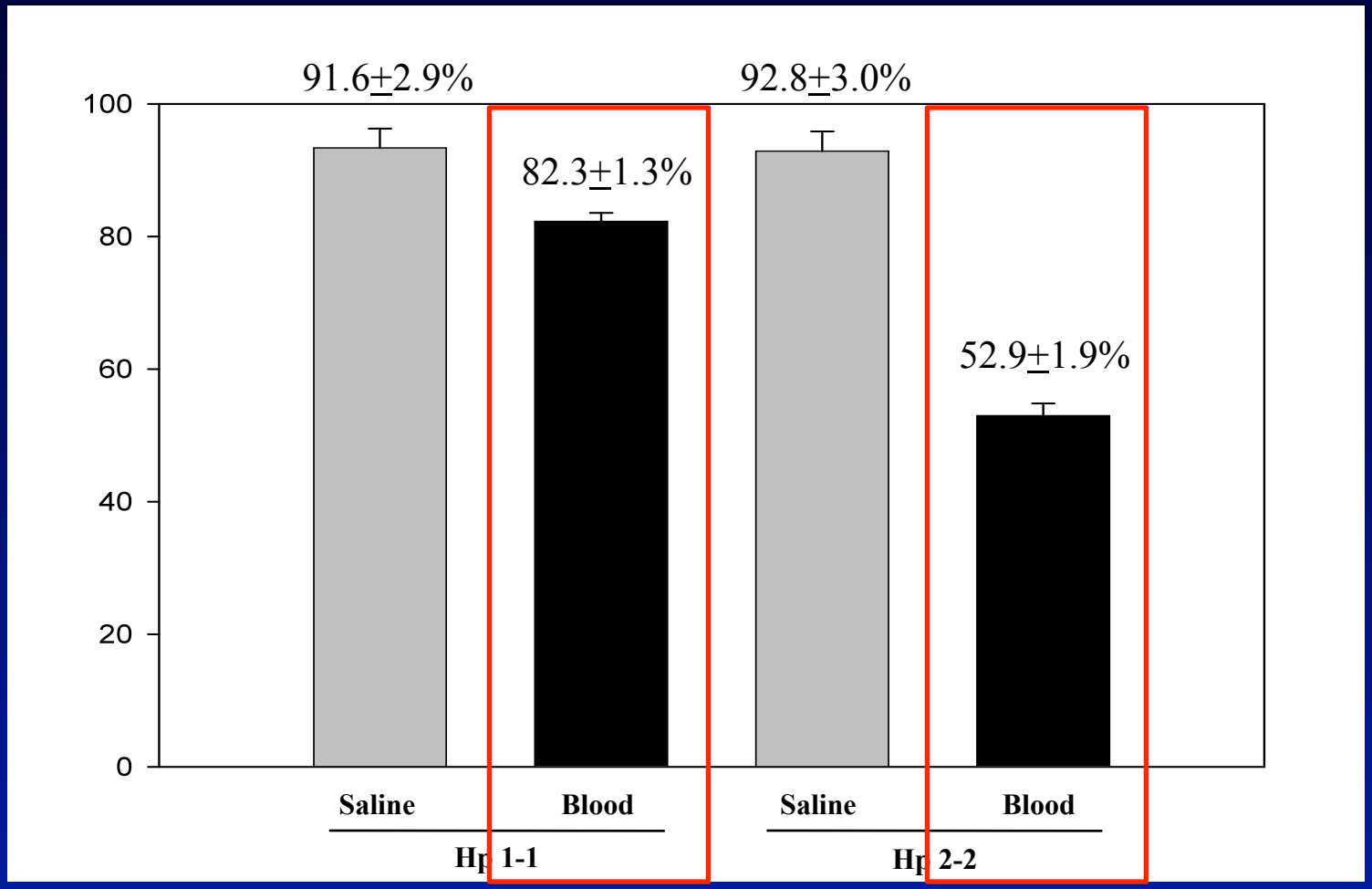
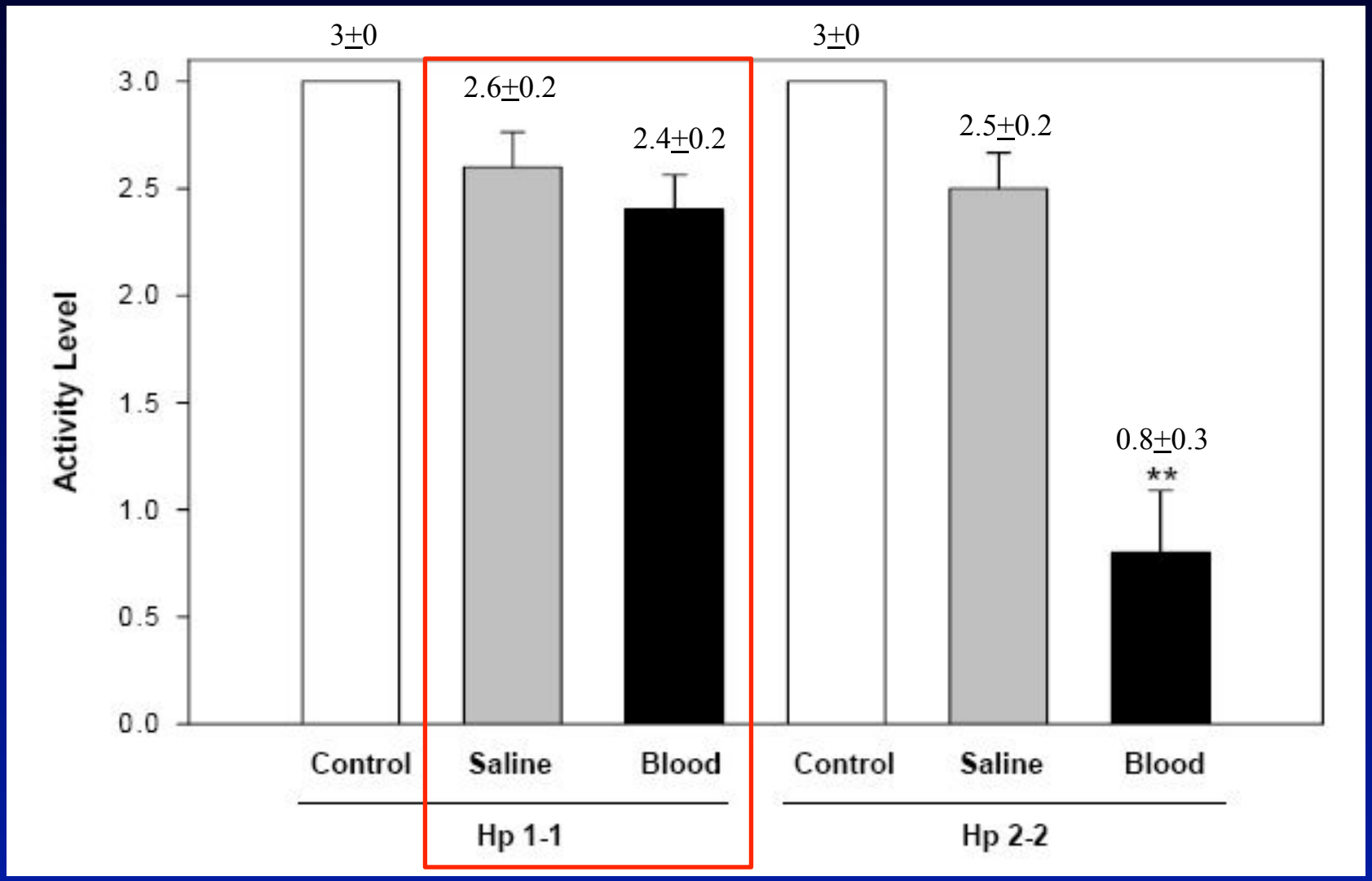


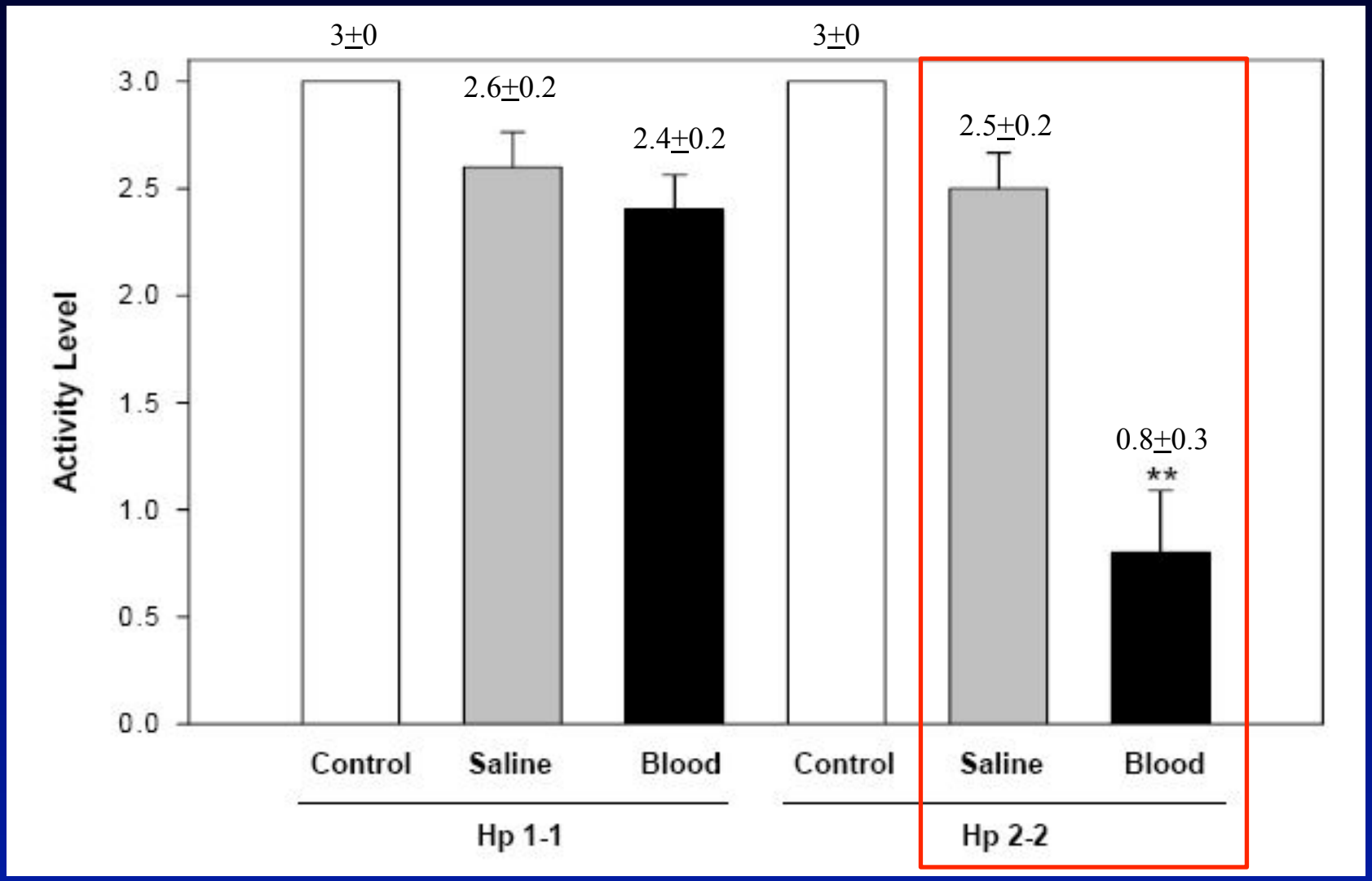
$p<0.001$

Results: Activity Level Analysis



NS (p=0.08)

Results: Activity Level Analysis



$p<0.001$

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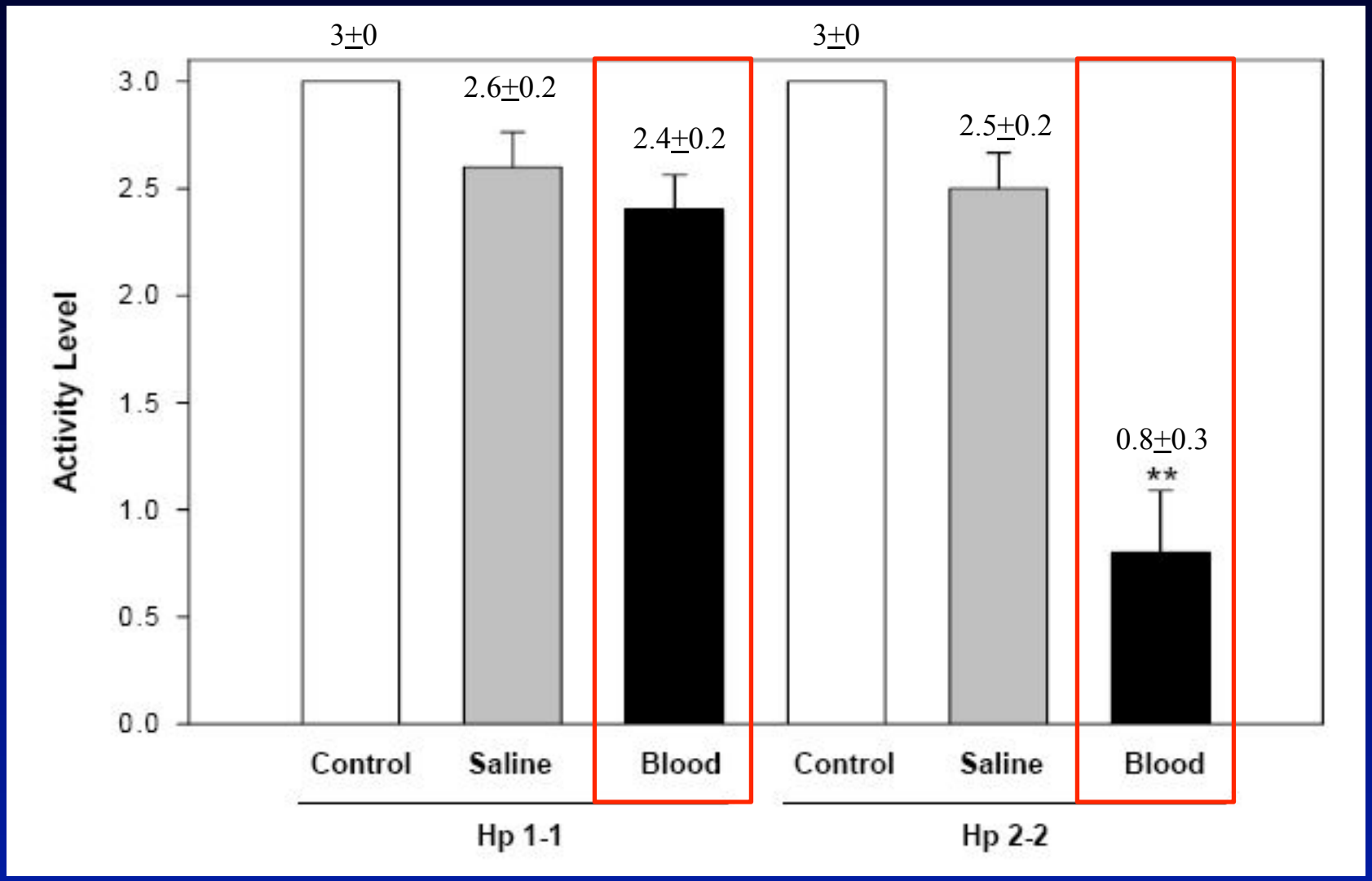
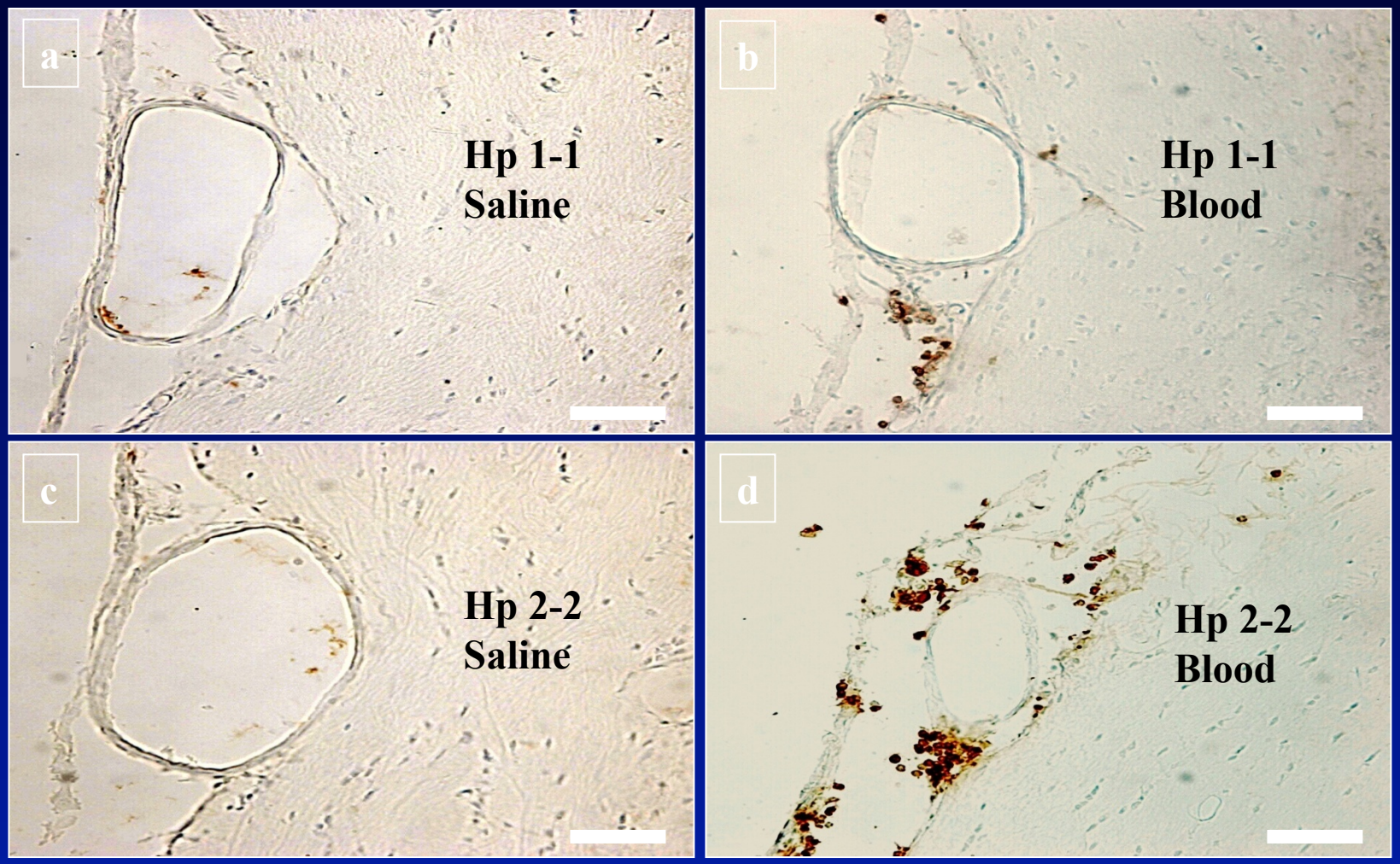


$p<0.001$

Results: Leukocyte Infiltration Measurements



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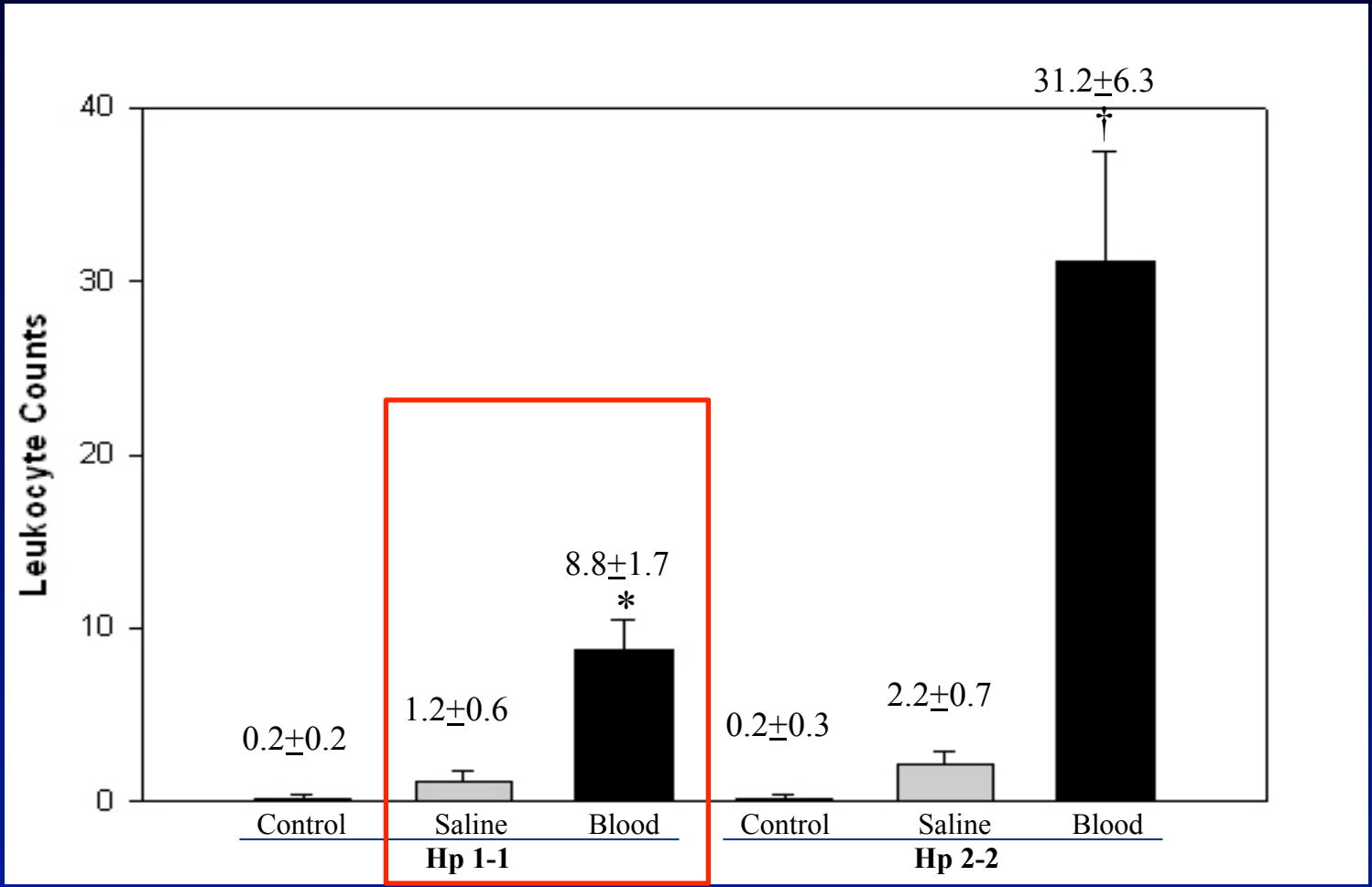
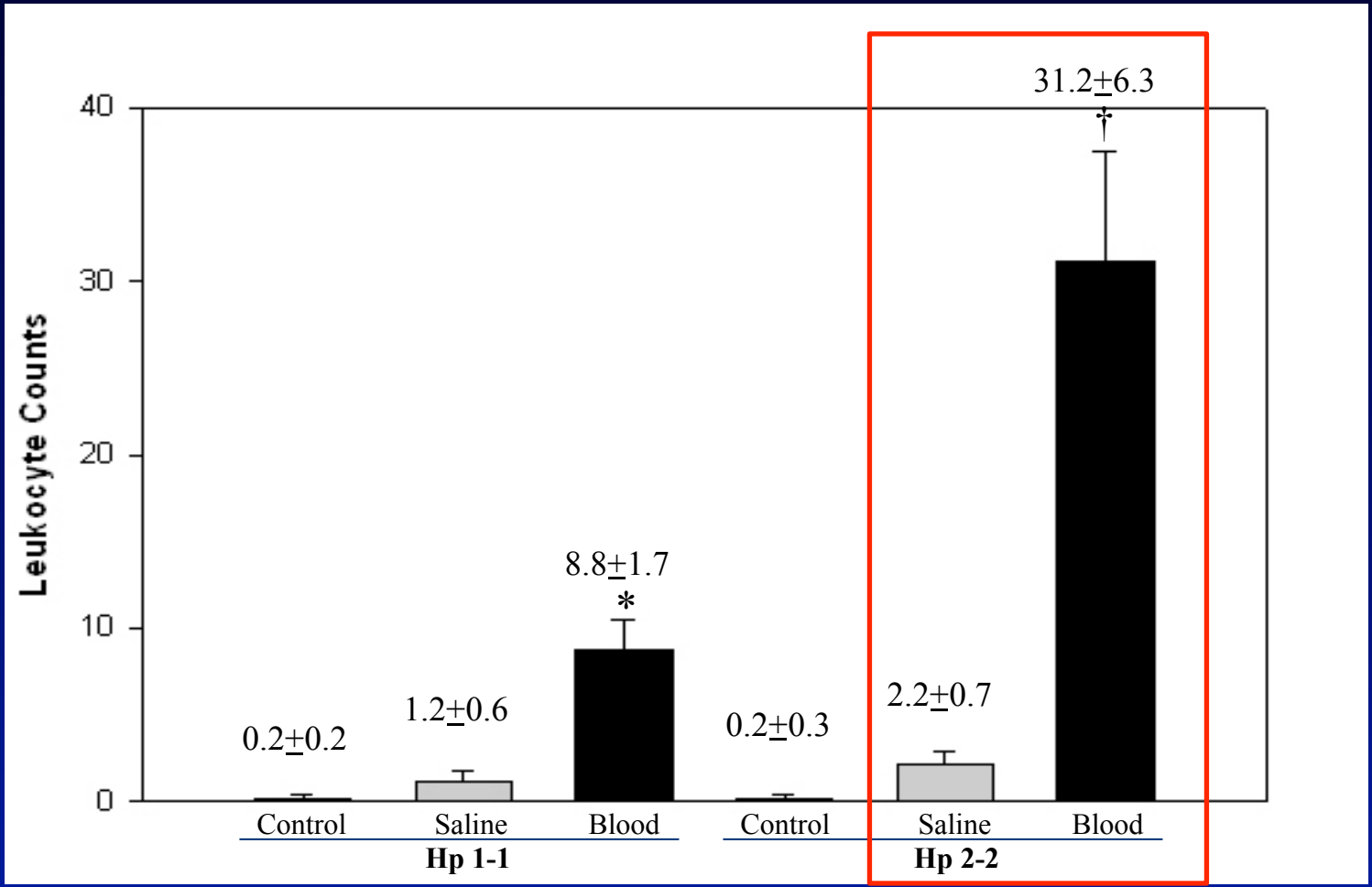


p<0.004

Results: Leukocyte Infiltration Measurements



p<0.002

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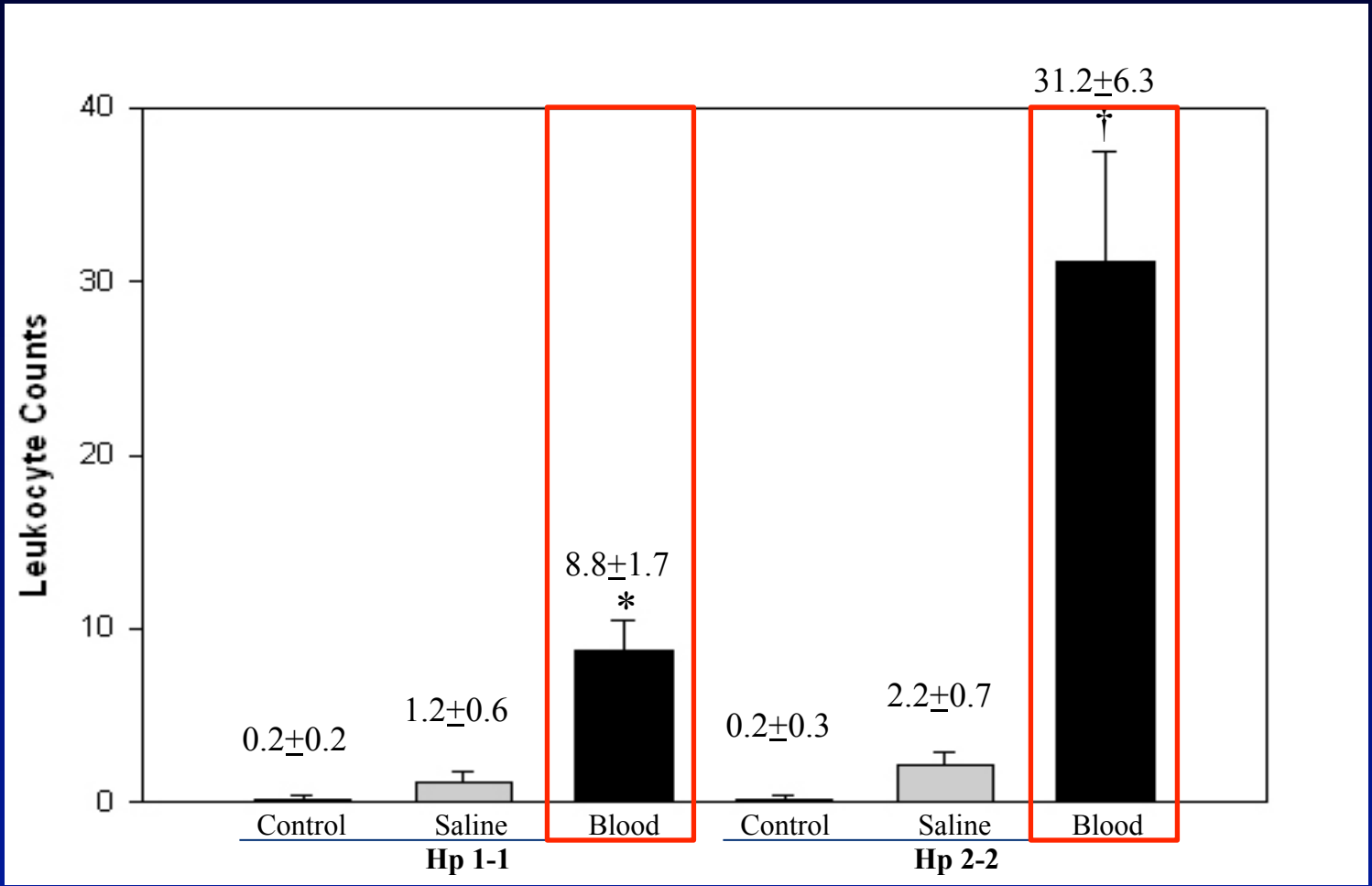


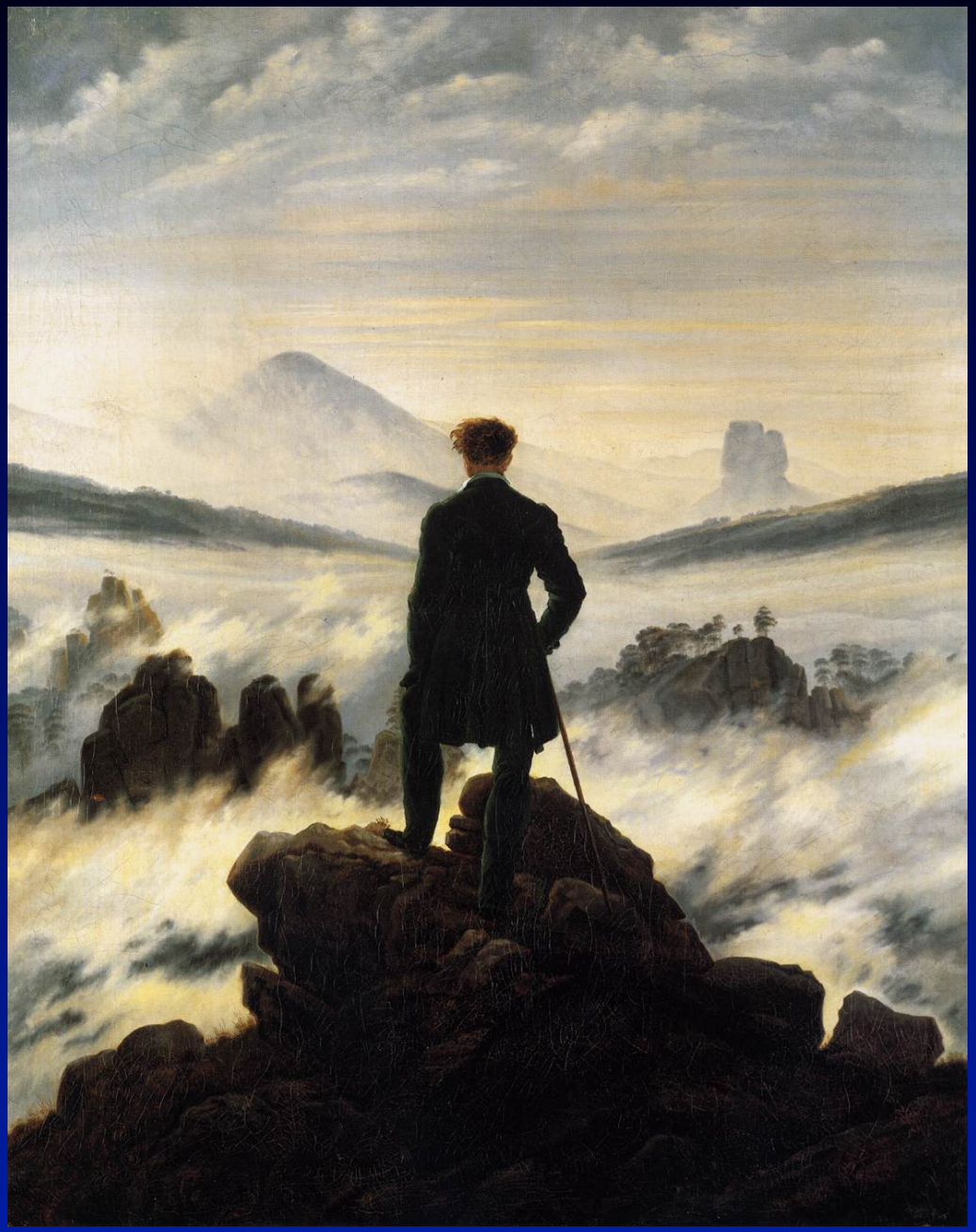
$p<0.009$

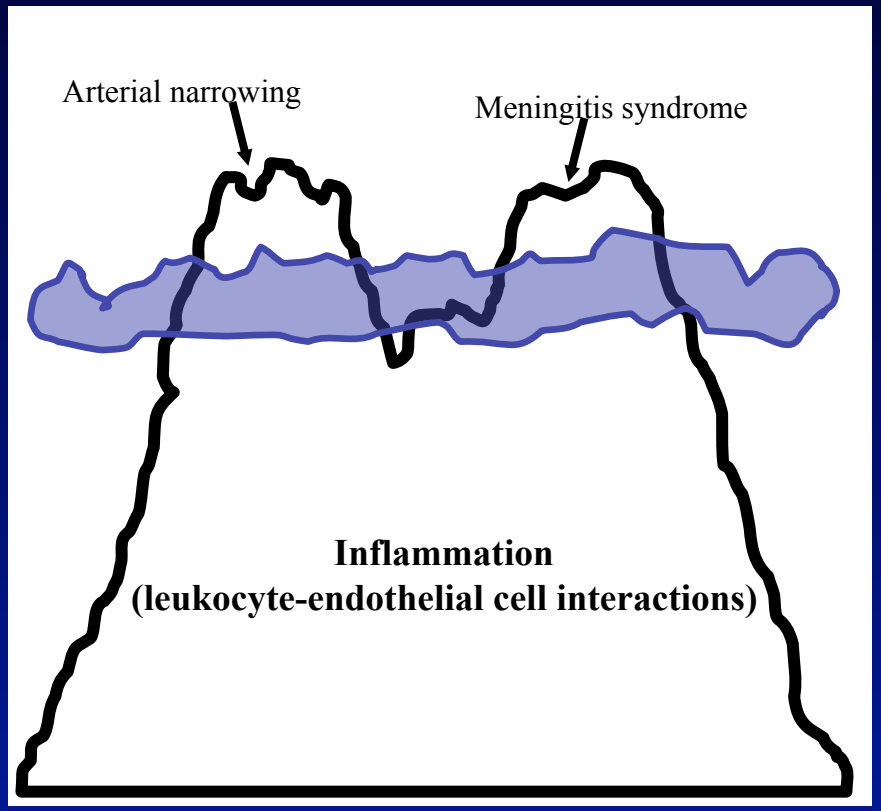
Haptoglobin and the development of cerebral artery vasospasm after subarachnoid hemorrhage

M. Borsody, MD, PhD; A. Burke, MD; W. Coplin, MD; R. Miller-Lotan, PhD; and A. Levy, MD, PhD

Abstract—*Background:* Vasospasm is a prolonged constriction of a cerebral artery that is induced by hemoglobin after subarachnoid hemorrhage (SAH). The subarachnoid blood clot also contains the protein haptoglobin, which acts to neutralize hemoglobin. Because the haptoglobin α gene is dimorphic, a person can expresses only one of three types of haptoglobin (α1–α1, α1–α2, or α2–α2) depending on the α subunit genes he or she inherits. Each of these three haptoglobin types has different antihemoglobin activities; therefore, haptoglobin may influence the development of vasospasm differently in various patients with SAH. *Objective:* To determine whether SAH patients who have haptoglobin containing the α2 subunit would be more likely to develop vasospasm than would be SAH patients who have haptoglobin α1–α1. *Methods and Results:* A total of 32 patients with Fisher Grade 3 SAH were enrolled in this study. Haptoglobin type was determined by polyacrylamide gel electrophoresis. The primary measure for vasospasm was increased blood flow velocities as detected by daily transcranial Doppler ultrasonography (TCD). The authors found that only 2 of 9 patients with haptoglobin α1–α1 (22%) had development of "possible" vasospasm as measured by TCD, whereas 20 of 23 patients with the haptoglobin α2 subunit (either the α1–α2 or α2–α2 haptoglobin types) had development of "possible" vasospasm (87%). The secondary measure for vasospasm was cerebral angiography performed between 3 and 14 days after SAH. Similar results (17% vs 56%) were seen between these groups in those patients who underwent cerebral angiography, although its inconsistent use limited the strength of the statistical comparison. *Conclusions:* Haptoglobins containing the α2 subunit seem to be associated with a higher rate of vasospasm than is haptoglobin α1–α1.

NEUROLOGY 2006;66:634–640



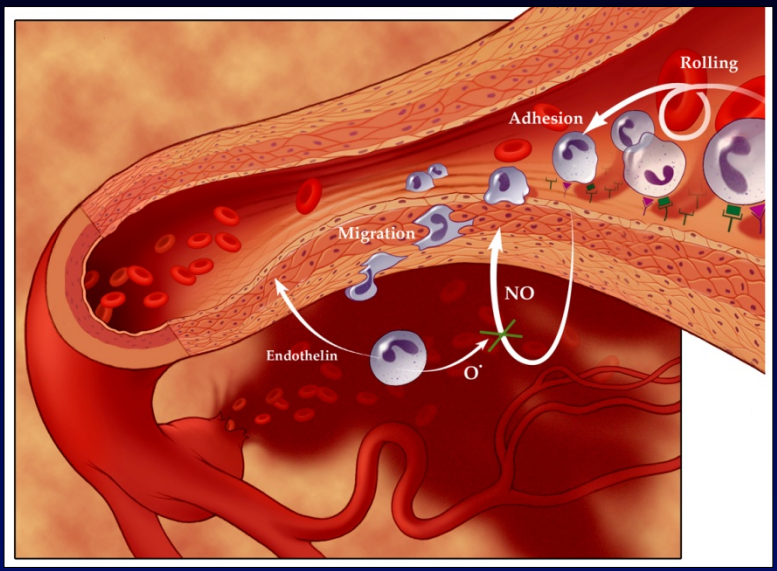

Arterial narrowing
Meningitis syndrome
Inflammation
(leukocyte-endothelial cell interactions)

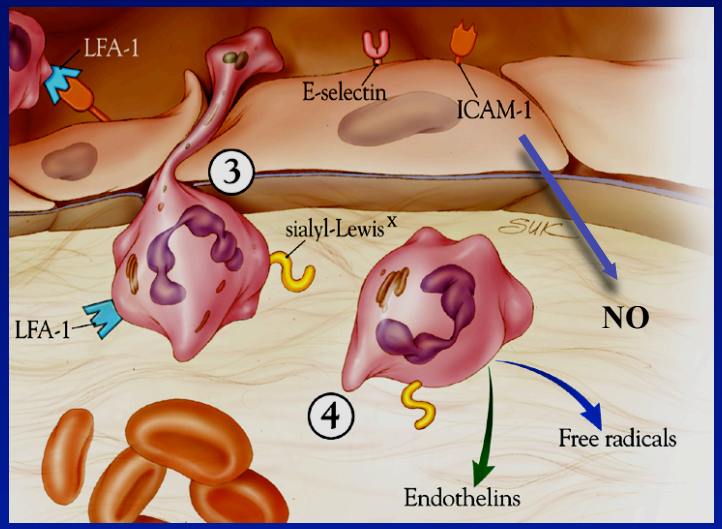
Conclusions

1. Arterial narrowing, ischemia, edema, meningeal irritation, etc., are manifestations of the root cause of vasospasm after SAH.

2. Inflammation (i.e., leukocyte-endothelial cell interactions) probably is the root cause of vasospasm.

3. Focusing on the immunobiology of vasospasm will lead to improved therapies.





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