# 뇌출혈: 병태생리와 진단 및 치료

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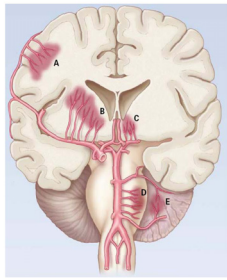
## Spontaneous intracerebral hemorrhage




- **Location of ICH**
  - Occurs in areas of the brain that are perfused by the perforating arteries that **arise directly** from the **large basal cerebral arteries**.
  - These perforating arteries are directly exposed to the effects of hypertension because they lack the protection normally afforded by a preceding gradual decrease in vessel caliber.

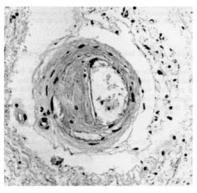
## Perforating arterial vessels

- **Arteries**
  - 100 – 400 μm
  - Internal elastic lamina (+)
  - Tunica media composed of 3 or 4 layers of smooth muscle cells
- **Arterioles**
  - < 100 μm
  - Internal elastic lamina (-)
  - Tunica media composed of 1 or 2 layers of smooth muscle cells

C. Miller Fisher
(1913 - 2012)

## Cerebral microangiopathy

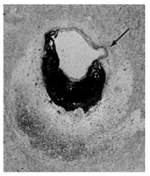
- **Microatheroma**
  - 300 – 700 μm
  - Subintimal proliferation of fibroblasts and deposits of lipid-laden macrophages
- **Lipohyalinosis**
  - 80 – 300 μm
  - Intermediate stage between the fibrinoid necrosis of severe hypertension and the microatheroma associated with more longstanding hypertension
  - Tunica media is thickened by deposits of connective tissue, particularly collagen and by accumulation of plasma protein
- **Microaneurysm**
  - Charcot and Bouchard in 1868
    1) Miliary saccular aneurysm: devoid of endothelial lining (40 – 100 μm)
    2) Lipohyalinotic aneurysm: depositis of hemosiderin pigments in the surrounding tissue (80 – 300 μm)
    3) Fusiform miliary aneurysm: 150 μm
    4) Pseudoaneurysm or bleeding globes



Microatheroma

Lipohyalinosis

Microaneurysm

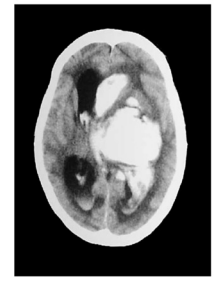


## Origin of ICH

- **Cole and Yates (1967)**
  - Hypertensive brains (n=100) and normotensive brains (n=100)
  - Strong circumstantial evidence for the relationship between hypertensive hemorrhage and microaneurysms
  - Microaneurysms existed in 46 of the hypertensives and 7 of the normotensives
  - Aneurysms and hematomas had a common topographic distribution in the brain.
- **Fisher (1971)**
  - Did not find support for aneurysms as the cause of the hemorrhages
  - ..... *"The same type of hypertensive vascular disease (lipohyalinosis) under some circumstances evokes ischemia and under others tends to bleeding"*

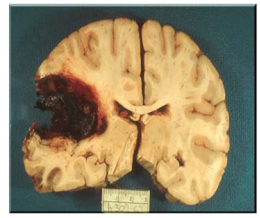
## Hematoma progression

- **A monophasic event?**
  - **Brott et al. (1997)**
    - Hematoma expanded in **26%** of the patients within 1 hour after the initial CT scan and in another **12%** within 20 hours.
  - **Kazui et al. (1996)**
    - Hematoma expanded in 41 of 204 patients (**20%**)with ICH
    - Occurring in 36% of patients who presented within 3 hours after the onset of the hemorrhage and in 11% of those who presented more than three hours after the onset.
  - This expansion has been attributed to **continued bleeding** from the primary source and to the **mechanical disruption of surrounding vessels**.



## Mechanism of cell damage

- Mechanical disruption
- Peri-hematomal edema
- Peri-hematomal cell death
- Peri-hematomal ischemia
- BBB disruption

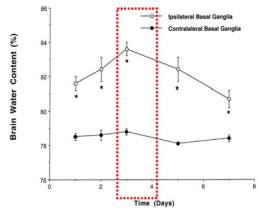


## Mechanical disruption

- **Mass effect due to expanding hematoma?**
  - Sinar et al. *(J Neurosurg 1987)*
    - A **mechanical microballoon** model to simulate ICH
    - Immediately following balloon inflation in the caudate nucleus of rats, there was a significant increase in intracranial pressure, accompanied by a reduction in CBF in the ipsilateral frontal cortex.
    - **No evidence of cerebral edema**
- The initial hemorrhage **dissects** along the white matter tissue planes of the brain, **encircling** islands of intact neural tissue.

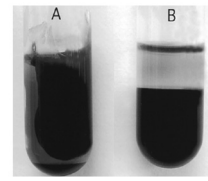
## Brain edema

- **Early phase (first several hours)**
  - Hydrostatic pressure and clot retraction
- **Second phase (first 2 days)**
  - Coagulation cascade and thrombin
- **Third phase (after 3 days)**
  - RBC lysis and Hemoglobin-induced toxicity




## Clot retraction

- **First several hours**
  - **Hydrostatic pressure**
  - **Clot retraction**
  - **Expulsion of serum from the clot**

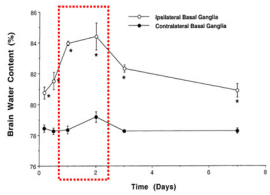


## Coagulation cascade

- **Second phase (first 2 days)**
  - Coagulation cascade and thrombin
- **Activation of coagulation cascade**
  - **Anticoagulated** autologous whole blood fails to produce perihematomal edema (Xi et al., 1998).
  - Streptokinase or tPA trials (Gebel et al., 1998; 2000)
    - **Reduction of edema in thrombolysis-induced ICH**
  - **No clot retraction**

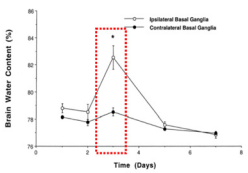
## Thrombin formation

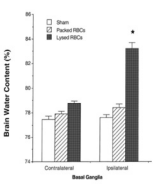
- **Thrombin**
  - A serine protease
  - Essential component in the clotting cascade
  - **A potent edema producer**
    - 5 U of thrombin: marked edema in rats
    - 260 – 360 U in the 1 mL blood
  - **Derived from prothrombin passed through BBB**
  - **Direct neurotoxicity**
    - Inflammation, seizure, scar formation, reactive gliosis
    - Cytotoxic edma, apoptosis




## RBC lysis

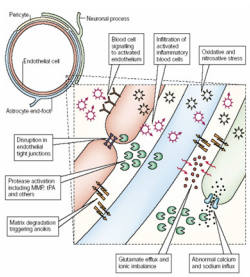
- **Delayed edema**
  - Clinically edema peaks **between 3 and 7 days**
  - Clot retraction, coagulation cascade or thrombin: early phase
  - **Hemoglobin and its degradation product**
    - Further BBB disruption
  - Heme is degraded by HO-1
    - **Iron**
    - **Carbon monoxide**
    - **Biliverdin and bilirubin**
  - Toxic itself or enhancing free radical injury

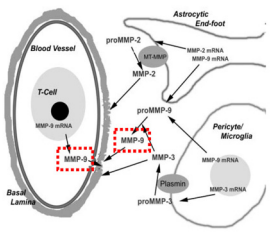



## BBB breakdown and MMP

- **Neurovascular unit and BBB**




## Molecular Signatures of Vascular Injury Are Associated With Early Growth of Intracerebral Hemorrhage

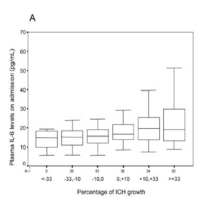
Yolanda Silva, MD; Rogelio Leira, MD; Javier Tejada, MD; José M. Lainez, MD; José Castillo, MD; Antoni Dávalos, MD; by the Stroke Project, Cerebrovascular Diseases Group of the Spanish Neurological Society

*Stroke*. 2005;36:86-91.

**TABLE 2. Biochemical Markers in Blood of Vascular Injury and Inflammatory Reaction**

| | Non-EHG (n=129) | EHG (n=54) |
|---|---|---|
| IL-6, pg/mL | 15.9 [11.5; 19.8] | 19.6 [13.6; 29.9] |
| TNF-α, pg/mL | 8.7 [4.7; 13.5] | 13.5 [8.4; 30.5] |
| MMP-9, ng/mL | 70.6 [47.8; 103.8] | 153.3 [117.7; 204.7] |
| C-Fn, μg/mL | 2.8 [1.6; 4.2] | 8.8 [6.2; 12.5] |

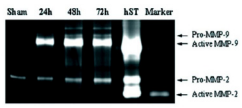
Numbers in square brackets are quartiles.
All comparisons, $P<0.001$.

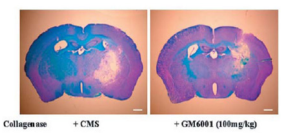


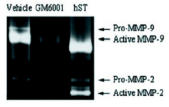

## Neuroprotection by inhibition of matrix metalloproteinases in a mouse model of intracerebral haemorrhage

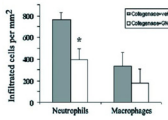
Jian Wang and Stella E. Tsirka

*Brain* (2005)
Brain Advance Access published March 30, 2005



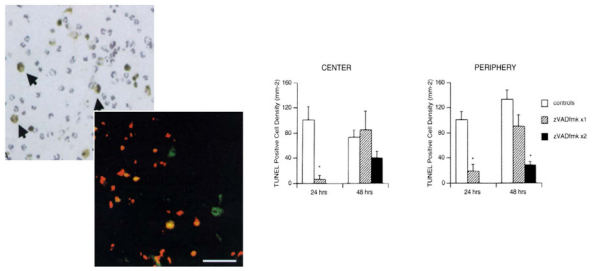
## Perihematomal cell death

Original Article

*Journal of Cerebral Blood Flow & Metabolism* (2000) **20**, 396–404

Evidence for Apoptosis After Intracerebral Hemorrhage in Rat Striatum

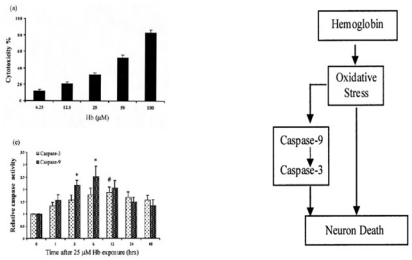
Kohji Matsushita[1], Wei Meng[1], Xiaoying Wang, Minoru Asahi, Kazuko Asahi, Michael A Moskowitz and Eng H Lo




## Hemoglobin-Induced Cytotoxicity in Rat Cerebral Cortical Neurons

### Caspase Activation and Oxidative Stress

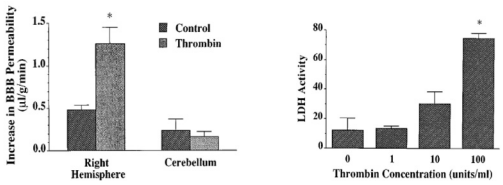
Xiaoying Wang, PhD; Tatsuro Mori, MD, PhD; Toshihisa Sumii, MD; Eng H. Lo, PhD



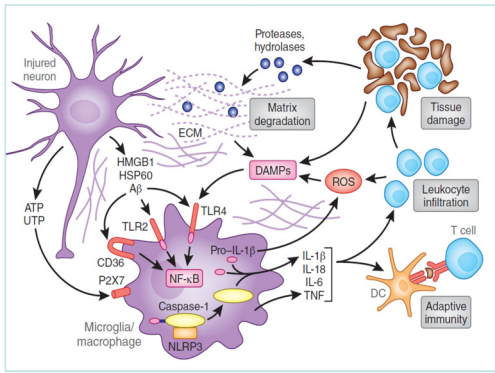

Mechanisms of edema formation after intracerebral hemorrhage: effects of thrombin on cerebral blood flow, blood-brain barrier permeability, and cell survival in a rat model

KEVIN R. LEE, M.D., NOBUYUKI KAWAI, M.D., SEOUNG KIM, B.A., OREN SAGHER, M.D., AND JULIAN T. HOFF, M.D.

*J Neurosurg* 86:272–278, 1997



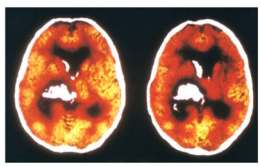

## Inflammation




*Nat Med 2011*

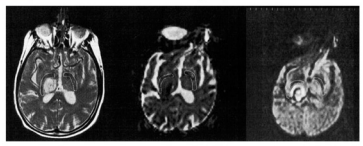
## Peri-hematomal ischemia?

- **CBF reduction**



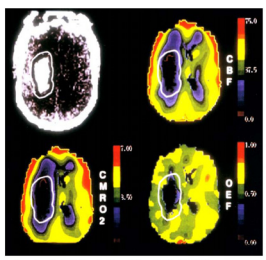
*Mayer et al. (Stroke 1998)*

- **No ischemic injury**

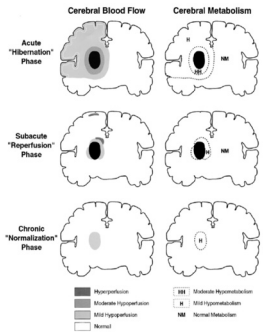


*Schellinger et al. (Stroke 2003)*

- **Reduced OEF**

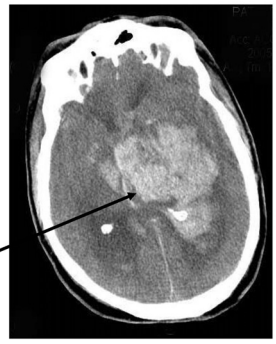



*Zazulia et al. (J Cereb Blood Flow Metab 2001)*



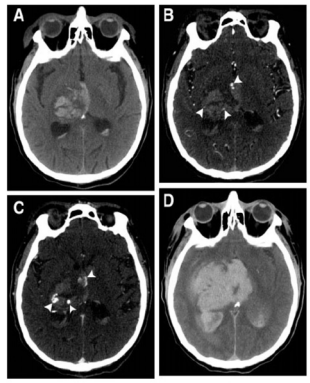
## Neuroimaging of ICH

- Computed tomography (CT) scan showing Left hemisphere intracerebral hemorrhage (ICH) with intraventricular extravasation




## CTA: spot sign

- CT contrast extravasates into hematoma
  - Spot sign, white arrows
- May predict hematoma expansion

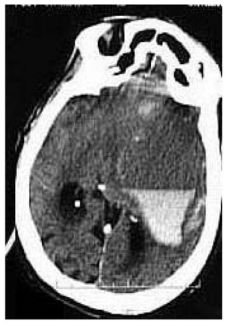



*Delgado Almandoz et al. Stroke, 40 (9): 2994. 2009*

## Imaging: AHA/ASA CPG

| | |
|---|---|
| **Rapid neuroimaging with CT or MRI** is recommended to distinguish ischemic stroke from ICH | Class I, Level of Evidence A |
| **CT angiography and contrast-enhanced CT** may be considered to help identify patients at risk for **hematoma expansion** | Class IIb, Level of Evidence B |
| **CT angiography, CT venography, contrast-enhanced CT, contrast-enhanced MRI, MRA and MRV** can be useful to evaluate for underlying structural lesions including **vascular malformations and tumors** when there is clinical or radiologic suspicion | Class IIa, Level of Evidence B ***(New recommendation)*** |

## Anticoagulation-induced ICH



- Anticoagulation leads to more hematoma growth and higher mortality
  - **Reverse warfarin promptly and aggressively**
  - **FFP or prothrombin complex concentrates (PCCs)**
  - **IV vitamin K**
    - Faster than SQ/PO but a small risk of anaphylactoid reaction

## Anticoagulation-ICH: AHA/ASA CPG

| | |
|---|---|
| Patients with a severe coagulation factor deficiency or severe thrombocytopenia **should receive appropriate factor replacement therapy or platelets**, respectively | Class I, Level of Evidence C *(New Recommendation)* |
| Patients with ICH whose INR is elevated due to OAC's should have their warfarin withheld, receive **therapy to replace vitamin K-dependent factors and correct the INR, and receive intravenous vitamin K** | Class I, Level of Evidence C |
| **PCCs** have not shown improved outcome compared with FFP but may have fewer complications compared with FFP and are reasonable to consider as an alternative to FFP | Class IIa, Level of Evidence B |
| The usefulness of platelet transfusions in ICH patients with a history of antiplatelet use is unclear and is considered investigational | Class IIb, Level of Evidence B *(New Recommendation)* |

## Recombinant Activated Factor VII

- rFVIIa, NovoSeven©
- Used for hemophilia
- Induces local hemostasis when it binds to tissue factor
  - The complex can activate Factors IX and X
  - Factor Xa helps convert prothrombin to thrombin

## FAST trial: failed

- A **phase II** randomized trial showed that treatment with rFVIIa within four hours after ICH onset
  - limited hematoma growth
  - **improved clinical outcomes** relative to placebo
  - increased frequency of thromboembolic events (7% vs. 2%)
- A subsequent **phase III** study comparing placebo to 20 μg/kg and 80 μg/kg of rFVIIa:
  - both doses diminished hematoma enlargement
  - **failed to show differences in clinical outcome**
  - Overall serious thromboembolic adverse event rates were similar, the higher rFVIIa (80 μg/kg) group had significantly more arterial events than placebo.

*Mayer SA, et al for the FAST Trial Investigators., N Engl J Med. 2008 May 15;358(20):2127-37.*
*Mayer SA for the FAST Trial Investigators. N Engl J Med. 2005 Feb 24;352(8):777-85.*

## BP target: INTERACT

- 404 ICH pts, randomized into:
  - **Target SBP of 140mmHg within 1 hr OR**
  - **Target SBP of 180mmHg**
- No increase in adverse events related to BP-lowering
- **Trend towards lower hematoma growth**
- **No differences in clinical outcome/QOL**
  - Not powered for clinical endpoints
- ATACH trial is on-going.

*Anderson CS, et al. Lancet Neurol. 2008;7(5):391-399.*

## BP target : AHA/ASA CPG

| | |
|---|---|
| Until ongoing clinical trials of BP intervention for ICH are completed, physicians must manage BP on the basis of the present incomplete efficacy evidence. | Class IIb, Level of Evidence C |
| **In patients presenting with a systolic BP of 150-220 mmHg, acute lowering of systolic BP to 140 mmHg is probably safe.** | Class IIa, Level of Evidence B ***(New recommendation)*** |

## BP lowering speed

- **If SBP is >200 mmHg or MAP is >150 mm Hg**, then consider **aggressive reduction** of BP with continuous intravenous infusion, with frequent BP **monitoring every 5 minutes**.
- **If SBP is >180 mmHg or MAP is >130 mm Hg and there is the possibility of elevated ICP**, then **consider monitoring ICP** and **reducing BP using intermittent or continuous intravenous medications while maintaining a CPP ≥ 60 mmHg.**
- **If SBP is >180 mmHg or MAP is >130 mm Hg** and there is not evidence of elevated ICP, then consider a **modest reduction of BP** using intermittent or continuous intravenous medications to control blood pressure, and clinically **reexamine the patient every 15 minutes**.

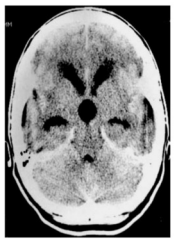
## Seizure and AED

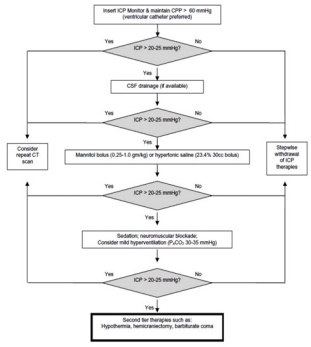
| | |
|---|---|
| **Clinical seizures should be treated** with anti-epileptic drugs | Class I, Level of Evidence A |
| **Continuous EEG monitoring** is probably indicated in ICH patients with depressed mental status out of proportion to the degree of brain injury | Class IIa, Level of Evidence B |
| **Prophylactic anticonvulsant medication should "NOT" be used.** | Class III, Level of Evidence B |

## Others, but important !

| | |
|---|---|
| Initial monitoring and management of ICH patients should take place in **an intensive care unit** with physician and nursing neuroscience intensive care expertise | Class I, Level of Evidence B |
| **Glucose should be monitored and normoglycemia is recommended** | Class I, level of Evidence C |
| Patients with ICH should have **intermittent pneumatic compression** for prevention of venous thromboembolism in addition to **elastic stockings** | Class I, Level of Evidence B |
| After documentation of cessation of bleeding, **low-dose subcutaneous low-molecular-weight heparin** or **unfractionated heparin** may be considered for prevention of venous thromboembolism in **patients with lack of mobility after 1 to 4 days from onset** | Class IIb, Level of Evidence B |

## Hydrocephalus: IICP control






*Adapted from Brain Trauma Head Injury Guidelines. Brain Trauma Foundation. 2000.*

## Surgery: STICH trial

- 902 ICH pts randomized trial of early hematoma evacuation (<96 hrs) vs medical
- **If ICH >1 cm from cortical surface, OR GCS ≤ 8**
  - Surgical patients tended to do **worse than medical**
- **If ICH < 1cm from surface**
  - Trended toward better outcomes with surgery, but not significant (OR 0.69, 95% CI 0.47-1.01)

*Mendelow AD, et al for the STICH Investigators. Lancet 2005;365(9457):387-397*

## Surgery: AHA/ASA CPG

| | |
|---|---|
| For most patients with ICH, **the usefulness of surgery is uncertain.** | Class IIb, Level of Evidence |
| Patients with **cerebellar hemorrhage who are deteriorating neurologically** or who have **brain stem compression and/or hydrocephalus from ventricular obstruction** should undergo **surgical removal** of the hemorrhage **as soon as possible**. | Class I, Level of Evidence B |
| Initial treatment of these **cerebellar hemorrhage** patients with **ventricular drainage** alone rather than surgical evacuation is **not recommended**. | Class III, Level of Evidence C |

## Surgery: AHA/ASA CPG

| | |
|---|---|
| For patients presenting with **lobar clots >30 cc and within 1 cm of the surface**, evacuation of supratentorial ICH by standard craniotomy **might be considered.** | Class IIb, Level of Evidence B |
| The effectiveness of **minimally invasive clot evacuation** utilizing either stereotactic or endoscopic aspiration with or without thrombolytic usage is **uncertain** and is considered investigational. | Class IIb, Level of Evidence B |
| While theoretically attractive, **no clear evidence** at present indicates that **ultra-early removal** of supratentorial ICH improves functional outcome or mortality rate. Very early craniotomy may be harmful due to increased risk of recurrent bleeding. | Class III, Level of Evidence B |

## Recurrent ICH: risk factors

- Lobar ICH
- Older age
- Apo E ε2 or ε4 alleles
- **Increased number of "microbleeds"**
- **Advanced WMLs**
- **High BP**
- **Anticoagulation**

*Lee SH et al., Stroke 2001; Neurology 2004; Neurology 2008; Neurology 2012*

## Prevention of recurrence

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|---|---|
| After the acute ICH period, **a goal target or a normal BP of < 140/90 (<130/80 if diabetes or chronic kidney disease)** is reasonable. | Class IIa, Level of Evidence B |
| **Avoidance of long-term anticoagulation** as treatment for **nonvalvular atrial fibrillation** is probably recommended following spontaneous **lobar ICH** because of the relatively high risk of recurrence. | Class IIa, Level of Evidence B |
| **Anticoagulation** following **nonlobar ICH** and **antiplatelet therapy** following **all ICH** might be considered, particularly when there are definite indications for these agents. | Class IIb, Level of Evidence B |