Aneurysmal Subarachnoid Haemorrhage

(*aSAH*)

Neurological complications with a focus on vasospasm

Professor Anthony McLean
Sydney University
Nepean Hospital
Sydney, Australia

Aneurysmal Subarachnoid Haemorrhage

- SAH only 5% all strokes
- 9:100,000 person years
- 50% people < 55 years age
- 1:6 die at time of bleed
- 70% die overall or require substantial help with daily living

- Secondary DCI occurs in 30% patients
- Poor outcome in half of these
- Peak period 4-10 days post bleed

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CRITICAL CARE

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Subarachnoid hemorrhage: who dies, and why?

Hector Lantigua[1†], Santiago Ortega-Gutierrez[2†], J. Michael Schmidt[1], Kiwon Lee[3], Neeraj Badjatia[4], Sachin Agarwal[1,5], Jan Claassen[1,5], E. Sander Connolly[5] and Stephan A. Mayer[6*]

Methods: We studied 1200 consecutive SAH patients prospectively enrolled in the Columbia University SAH Outcomes Project between July 1996 and January 2009. Analysis was performed to identify predictors of in-hospital mortality.

Results: In-hospital mortality was 18 % (216/1200): 3 % for Hunt-Hess grade 1 or 2, 9 % for grade 3, 24 % for grade 4, and 71 % for grade 5. The most common adjudicated primary causes of death or neurological devastation leading to withdrawal of support were direct effects of the primary hemorrhage (55 %), aneurysm rebleeding (17 %), and medica complications (15 %). Among those who died, brain death was declared in 42 %, 50 % were do-not-resuscitate at the time of cardiac death (86 % of whom had life support actively withdrawn), and 8 % died despite full support.

Table 1 Mortality according to admission Hunt-Hess grade

Hunt-Hess grade	Dead/Total, number	Proportion of study population, %	Mortality rate, %
1. Mild headache	12/342	19.5	3.5
2. Severe headache or cranial nerve deficit	6/186	15.5	3.2
3. Confusion, lethargy, or lateralized weakness	30/319	26.6	9.4
4. Stupor	41/173	14.4	23.6
5. Coma	127/180	15.0	70.5
Total	216/1200	100.0	18.0

Key messages

- In-hospital mortality in this single-center cohort study of patients with SAH was 18 %
- 42 % died of brain death, 50 % were DNR, and only 8 % died despite full medical support
- Direct effects of severe hemorrhage, rebleeding, and medical complications were the most common causes of death

Early Brain Injury

- acute pathological events that occur within 72 hours of aSAH
- begin minutes after the bleeding commences
- include –
  - cerebral autoregulation and blood brain barrier disruption
  - activation of inflammatory pathways
  - excitotoxicity
  - oxidative stress
  - apoptosis activation
- not limited only to primary site of haemorrhage
- many of these mechanisms also contribute to Delayed Cerebral Ischaemia (DCI)
  aka DIND =Delayed Ischaemic Neurological Damage

EBI Mechanisms:

1. Mechanical Injury and Cerebral Autoregulation Disruption. .
   eg. reactive constriction of supply artery
   early ICP elevation is common, causing reduction in CBF and CPF
2. Electrolyte disturbances.
   - Hyponatremia develops within 1-2 days after bleed (10-30% patients), caused by inappr secretion ADH
   - cellular calcium homeostasis is impaired
   - low magnesium in 40% patients
   - high serum K+ probably due to decreased K-Na pump mechanism
3. Excitotoxicity
   linked to interstitial glutamate concentration/altered synaptic transmission/BBB disruption
4. Nitric oxide alterations and Endothelin -1 Increase
5. Oxidative stress . SAH results in haemoglobin autooxidation and lipid peroxidation with a rapid consumption of enzymatic and nonenzymatic antioxidant defence mechanisms
6. Inflammatory. Febrile patients have worse outcome than nonfebrile(1955)
   higher serum IL-6 levels associated with DIND and worse clinical outcome
7. blood breakdown products
8. small vessel spasm
9. cortical spreading depolarization
10. cell death/ apoptosis

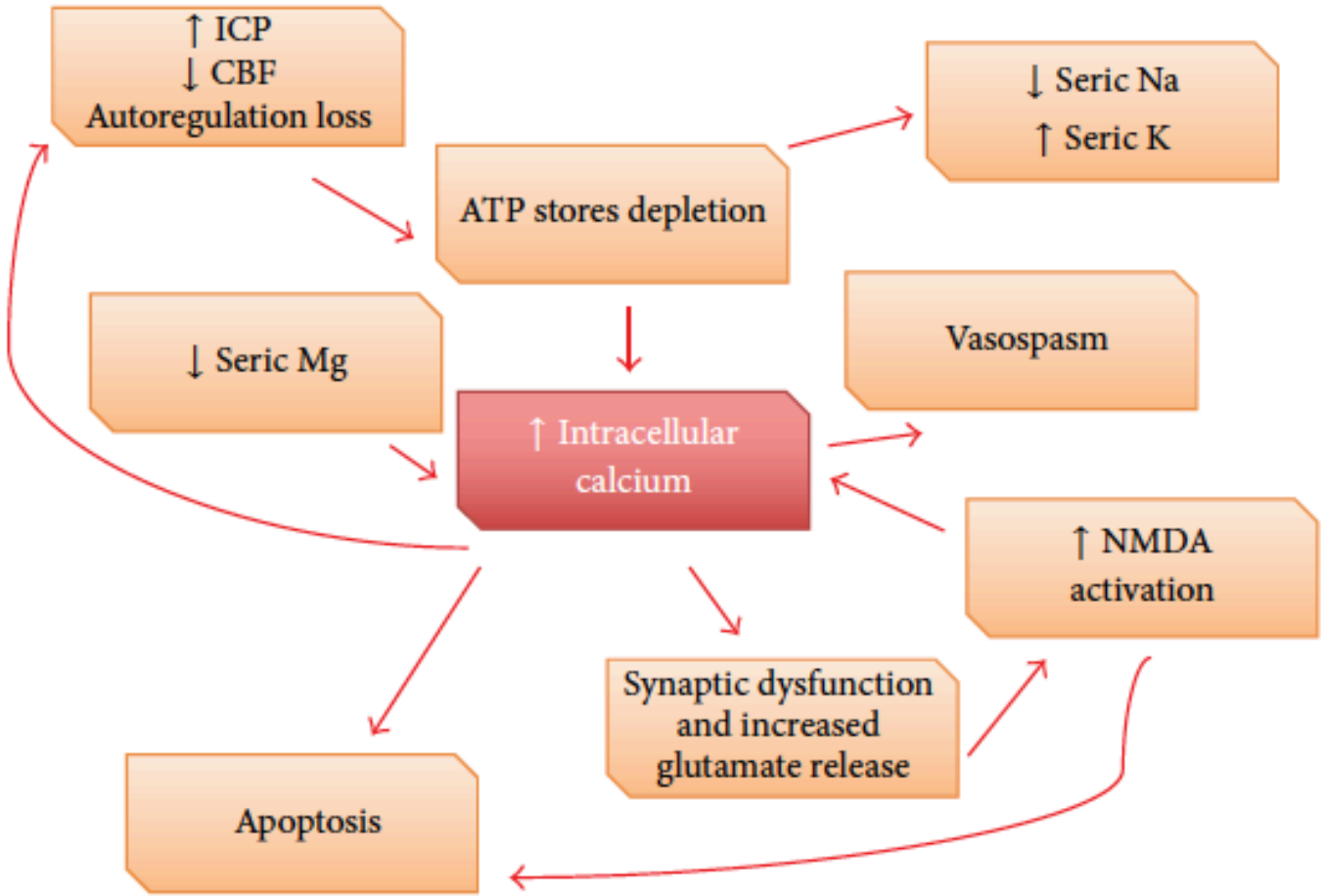

FIGURE 1

cellular calcium homeostasis is impaired

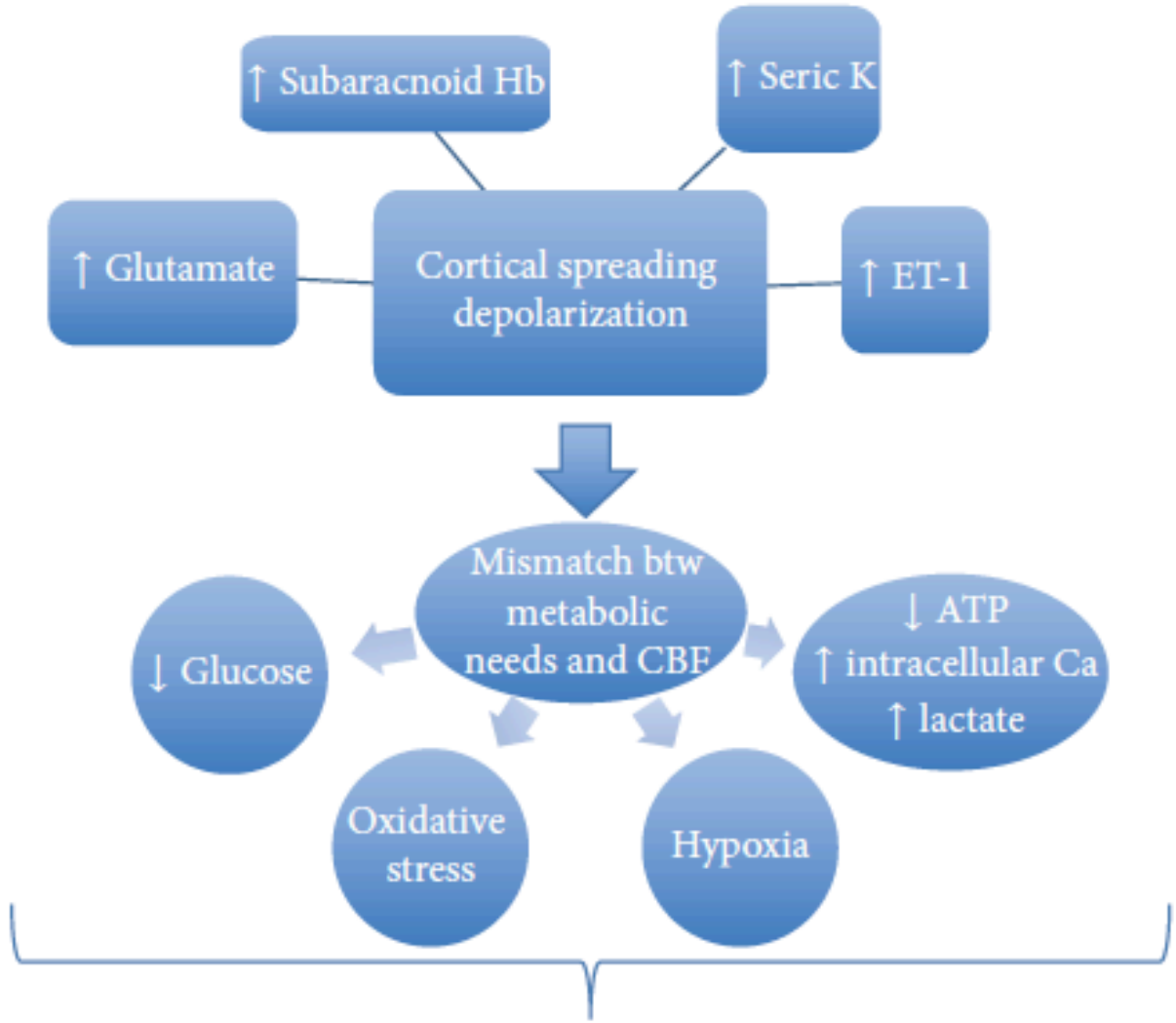
↑ Subaracnoid Hb
↑ Seric K
↑ Glutamate
Cortical spreading depolarization
↑ ET-1
Mismatch btw metabolic needs and CBF
↓ Glucose
↓ ATP
↑ intracellular Ca
↑ lactate
Oxidative stress
Hypoxia
Neuronal death and cortical spreading ischemia

FIGURE 2

Delayed Brain Injury

Describes critical events arising in the late phase of aSAH 3-14 days

Mechanisms:

1. Delayed cerebral vasospasm
2. Microcirculation Dysfunction and Vasospasm
3. Cortical Spreading Ischaemia

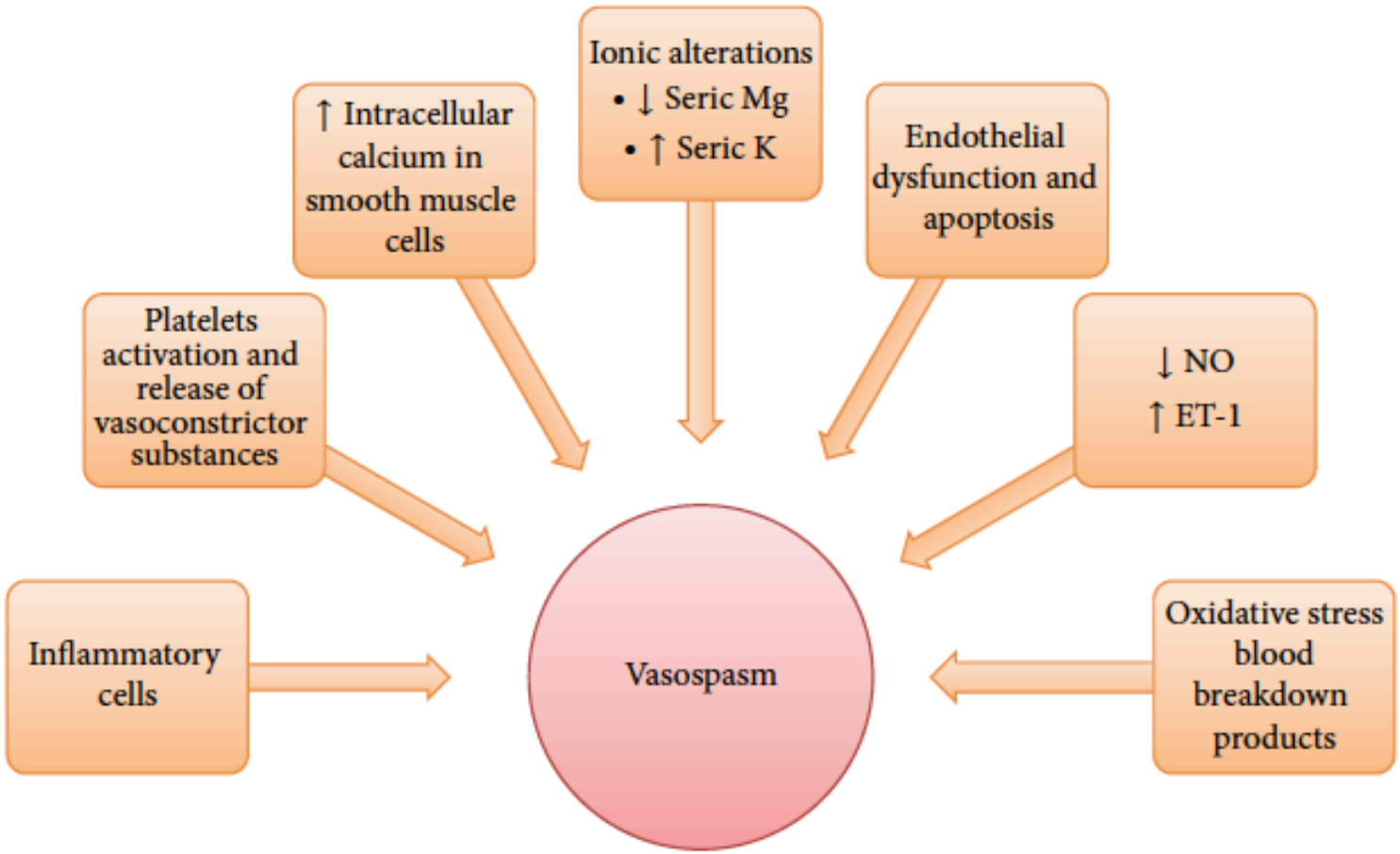
Ionic alterations
• ↓ Seric Mg
• ↑ Seric K
↑ Intracellular calcium in smooth muscle cells
Endothelial dysfunction and apoptosis
Platelets activation and release of vasoconstrictor substances
↓ NO
↑ ET-1
Inflammatory cells
Vasospasm
Oxidative stress blood breakdown products

FIGURE 3

Treatment Strategies for vasospasm

1. Triple H therapy: hypertension~~, hypervolaemia, hemodilution~~
   a moderate CPP 80-120 mm Hg is an effective method of improving cerebral autoregulation

2. Calcium channel blockers:
   nimodipine, an L-type CCB the only pharmacological agent demonstrating an improvement in neurological outcome (0-21 days),doesn't have a real effect on cerebral vasospasm. ie it's effect is outside any effect on vasospasm

3. Magnesium sulfate: initial studies indicating benefit; subsequent clinical trials have not. Keep serum Mg on high side ?

4. ET-1 receptor Antagonists:ET-1 has role in vasospasm but CONSCIOUS -1 & -2 trials did not reveal benefit in blocking

5. Vasodilators: milrinone, oestrogens. Theoretically possible beneficial but inadequate clinical data.

6. NO donors: experimental studies in primates (NA nitrate, SNIP, nitrite) but very short T1/2 and toxicity

Treatment Strategies for vasospasm II

7. Antioxidants: ?? Rat model astaxanthin shows some promise

8. NSAIDs: contrasting results in studies. Possibly due to heterogeneity of inflammatory patterns identified

9. Antiplatelet agents and inhibitors of thrombosis: antiplatelets contrasting results.
   Role for ADAMTS-13 (inhibits thrombus formation) ?

10. Statins: conflicting results with none definitively demonstrating good benefit

Treatment Strategies for vasospasm

Endovascular:

a). Pharmacologic vasodilatation:
agents commonly used are verapamil, nicardipine, milrinone
all can cause hypotension (and fall in CPP) and have a short duration of benefit
continuous nimodipine via microcatheter in ECA for 9-15 days. Looks promising.

b). Balloon angioplasty
first tried in 1984
no benefit demonstrated and carries risk of vessel rupture

Table 4 Relationship of medical and neurological complications to in-hospital mortality

	Survivors	Non-survivors	Univariate/Unadjusted			Multivariate/Adjusted[a]		
			OR	95 % CI	*P* value	OR	95 % CI	*P* value
Delayed cerebral ischemia								
Symptomatic vasospasm without infarct	104 (11)	14 (7)	0.6	0.3–1.0	0.095	0.5	0.3–1.0	0.06
Symptomatic vasospasm with infarct	64 (7)	21 (10)	1.5	0.9–2.6	0.004	1.9	1.0–3.7	0.07
No symptomatic vasospasm with infarct	23 (2)	13 (6)	2.7	1.3–5.4	0.000	2.2	0.8–5.8	0.13

Values are presented as number (percentage)

Discussion:

- DCI is a complex process with multiple pathological pathways, leading determinant of poor functional outcome in patients surviving initial haemorrhagic insult
- Vasospasm role in poor outcome may be overemphasized
- Vasospasm not necessary a perquisite for DIND development
- Reversal of vasospasm does not necessary help and is inadequate as a therapeutic marker. Outcome remains poor.
- Determinants for DIND seem to occur during the EBI phase and emphasis should be here

the end