In-house stroke
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Disclosure Information

Relationship with companies who manufacture products used in the treatment of the subjects under discussion
Yes____ No __x__ If "Yes," list company(ies) with the relationship(s) below.

Relationship	**Manufacturer(s)**
Research Support	___NIH/NINDS: K23 NS073104 Local PI: SOCRATES (Astra-Zeneca), PRISMS (Genentech), POINT (NIH-StrokeNet(
Speaker's Bureau	___None_____
Consultant	___Heartware Incorporated_____
Share Holder	___None_____
Other Financial Support	__Honoraria from American College of Physicians for MKSAP 18 Clinical end point committee (Claret, Edwards)
Large Gift(s)	____None_____

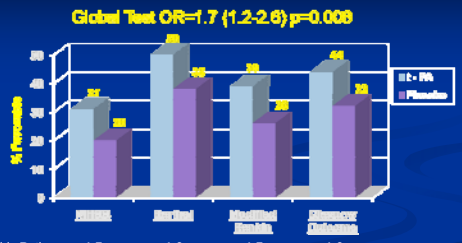
Relationships with any of the commercial supporters of this CME activity: N/A

Discussion of unlabeled uses: Yes _x____ No_____
-Use of intra-arterial tPA for acute stroke

What is the most common cause of in-hospital stroke?

- Post-cardiac surgery
- Post-carotid surgery
- Post-TIA
- Anticoagulation reversal

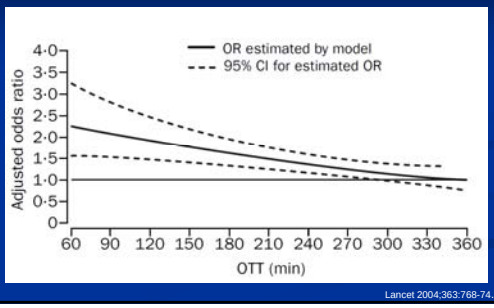
Outcome at 3 Months for Part 2 *NIH rt-PA Study*



Odds Ratio	1.7	1.6	1.7	1.6
95% CI	1.0-2.8	1.1-2.5	1.1-2.6	1.1-2.5
p value	0.033	0.026	0.019	0.025

NINDS tPA trial. NEJM **1995**

Meta-analysis of rt-PA-based Thrombolytic Trials
NINDS, ATLANTIS, & ECASS TRIALS



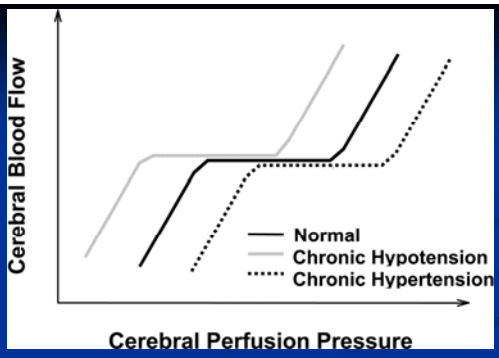
Lancet 2004;363:768-74.

In-hospital thrombolysis

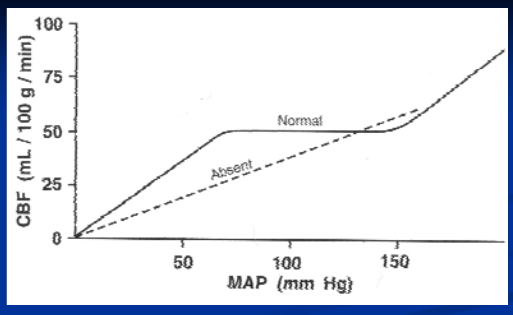
- Door to needle times are significantly delayed for the in-hospital stroke:
  - Delayed recognition
  - Delayed imaging acquisition
  - Availability of a bed for thrombolysis
  - Pharmacy stocking the pharmacy
- Smaller proportion of patients

Treatment Beyond 3 Hours

- Intra-arterial treatment previously reserved for a major vessel occlusion, or when tPA is contraindicated
  - 3-6 hours Intra-arterial thrombolytic studied in the PROACT study (JAMA 1999). Clinical benefits at 3 months
- Multiple clinical trials showed a clinical benefit

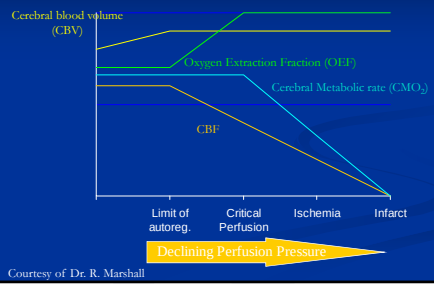


J App Physiology 2001; 1986-1994



Chapter 52, section 4, Neurosurgical anesthesia

Cerebral Response to Hypoperfusion



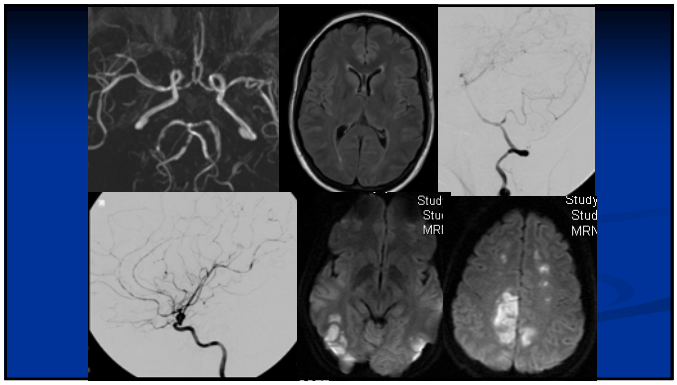
Courtesy of Dr. R. Marshall

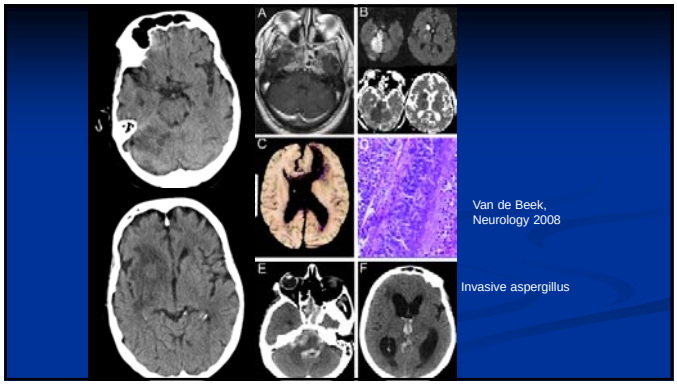
Transplant patient

- Medications:
  - Can lead to the posterior reversible vaso-constriction syndromes (part FK 506)
- CNS infections
  - Bacterial meningitis
  - Angio-invasive aspergillus

PRES/RCVS/etc

- Call-Fleming – post-partum angiopathy and other 1/1 syndromes
  - Abrupt HA/N/szs, strokes frequently occipital and in the borderzone
  - 2/2 syndromes: SAH spasm, carcinoid, hyperCa+2, severe **HTN**, Porphyria
- Eclampsia: as above, seizures, systemic dz
- Medication and drug induced
  - Transplant medications, SSRI, stimulants, IV-IG
- PRES is a complication of the RCVS (Chen, Ann Neurol 2010). Vessels tend to normalize at 3 months





Van de Beek, Neurology 2008

Invasive aspergillus

Bacterial Endocarditis

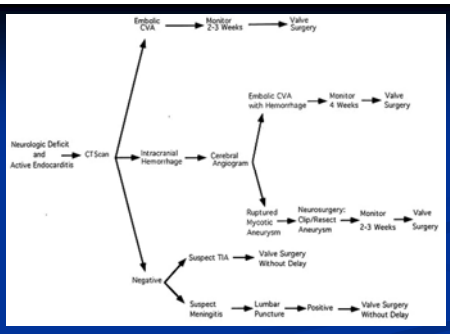
- Neurological manifestations present in 25% to 45% in many series. After one week on Abx, neurological complications are < 10%
- Mortality of 80% for ruptured mycotic aneurysms. These are rare.
- Complications:
  - Stroke (9-22%). Up to 75% at the time of admit
  - ICH/SAH in 2-8% (most **not** aneurysmal)
  - CNS infection: meningitis or abscess
- Embolic risk: On IV Abx risk of stroke 0.5%/d to 0.3%/d

Prabakharan. Continuum Neurology 2008

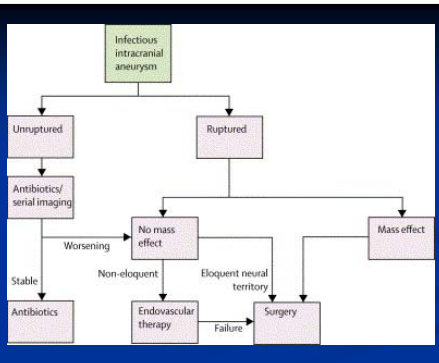
Bacterial Endocarditis

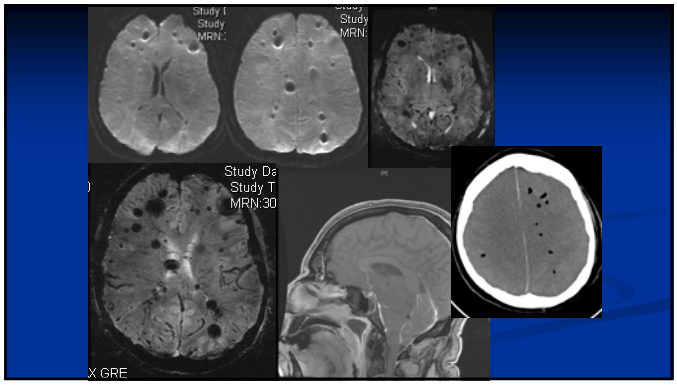
- Most mycotic aneurysms respond to treatment, angiography probably not warranted
- Indications for angiogram: ICH/SAH, risk assessment prior to cardiac surgery, focal neurological symptoms
- Mycotic aneurysms are usually small and distal – not well seen with CTA/MRA; GRE imaging
- Anti-thrombotics do not seem to affect the rate of embolization
- With mechanical valve, may need to A/C, but ICH risk can be very high with S. Aureus

Prabakharan. Continuum Neurology 2008



THE ANNALS OF THORACIC SURGERY





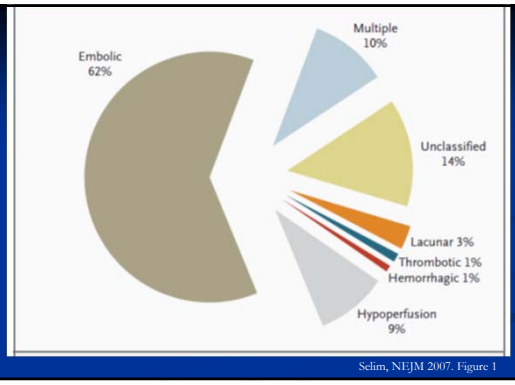
What is the most common cause of peri-operative stroke?

- Anesthesia
- Air embolism
- Hypoxic-ischemic injury
- Atrial embolism

Stroke after surgery

- In general risk of stroke after all surgeries is low except for vascular procedures
- Isolated CABG rate 1.4-3.8%
- Valve procedures up to 9.7%
- Aortic repair and dissection 3-6% spinal cord stroke
- Rates after CEA in CREST 2.3% vs 4.1% in CAS

  - Adapted from Selim, NEJM 2007; Mohr JP 5th edition



Selim, NEJM 2007. Figure 1

Mechanisms of stroke

- Most strokes are not from hypo-perfusion
- Peri-operative strokes most common on day #2, with cardio-embolic etiology most likely
- Stopping warfarin
- Rare causes:
  - Air embolism
  - Fat embolism
  - Paradoxical emboli
  - Dissection
- Risk factors: HTN, renal disease, cardiac disease, stroke, AF (Bateman, Anesthesiology 2009)

Selim, NEJM 2007

Special situations

- Spinal cord stroke:
  - Most often seen in context of aortic dissection
  - Presents with paraplegia / retention
  - Infarction at level of spinal cord watershed
  - Emboli to the lower thoracic cord
  - Likely benefit from prophylactic lumbar shunting – risk of subdural

Combined CEA and CABG

- High rates of peri-operative stroke with CABG with carotid stenosis
  - Stroke rate only appears higher among patients with *symptomatic* disease (Kougias, Ann Vasc Surg 2007)
- Simultaneous surgery seems intuitive
  - In Canada 0.5% of CABG were combined with CEA, with stroke and death rate being 2.6 times higher (Hill, Neurology 2005)
- RCT (n = 185) showed 8.8% rate of peri-operative stroke if CEA delayed versus combined procedure (1.0%) (Illuminati, J Vasc surg 2011).
  - The rates in the medical arm are unusually high, and most strokes are not due to the ICA (Naylor, J Vasc surg 2012)
  - Excluded patients with emergency procedures and aortic disease
- Staged procedure also appears safe (Santos, Ann Vasc surg 2012)

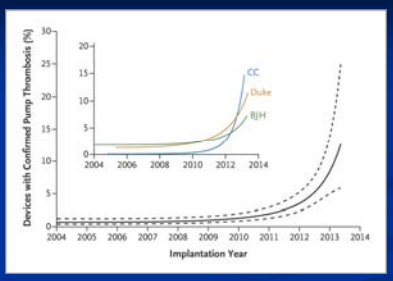
Mechanical circulatory support

- Risk factors for stroke (Kato, J Heart Lung Transpl 2012)
  - Prior stroke, malnutrition and inflammation, infection
  - Ischemic and hemorrhagic strokes often co-existed
  - Role of therapeutic a/c less clear
- Underlying AF and cardiac function (Nakajima Circ J 2011)
- Hemorrhagic stroke
  - Endocarditis should be suspected (Aggarwal ASAIO 2012)
  - Hemorrhagic transformation
  - Coagulopathy: often patients on aspirin, dipyridamole, and warfarin

Epidemiology of LVAD stroke

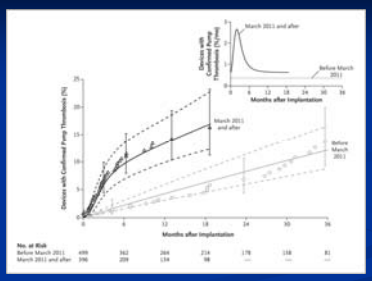
- Stroke is a leading causes of mortality
- INTERMACS reports (Kirklin, JHLT 2014)
- Heart Mate II clinical trials
  - 8% developed a hemorrhagic stroke
- HVAD trials: hemorrhagic stroke risk and reports with hypertension
- Other reports: generally 15% overall rate

Overall Occurrence of Confirmed Pump Thrombosis at 3 Months after HeartMate II Implantation.



Starling RC et al. N Engl J Med 2014;370:33-40.

Occurrence and Incidence of Confirmed Pump Thrombosis Stratified According to Implantation Date.



Starling RC et al. N Engl J Med 2014;370:33-40.

Risk factors for stroke

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  - Ischemic and hemorrhagic strokes often co-existed
  - Role of therapeutic a/c less clear
- Underlying AF and cardiac function (Nakajima Circ J 2011)
- Hemorrhagic stroke
  - Endocarditis should be suspected but rare (Aggarwal ASAIO 2012)
  - Hemorrhagic transformation
  - Coagulopathy? often patients on aspirin, dipyridamole, and warfarin

Risk factors ischemic stroke

- Pump thombosis
  - Surprisingly cases of pump thrombosis by INTERMACS definition do not have stroke
  - Our experience parallels this
- Aortic valve opening and thrombosis in the aorta and carotid due to flow type (Mehra, J Heart Lung Transpl 2014)
- Anticoagulation: neither necessary nor sufficient
- Large artery atherosclerosis: challenges in diagnosis

Risk factors hemorrhagic stroke

- Anticoagulation
- Cerebral amyloid angiopathy
  - Rare under age 55
  - Average age of stroke (54)
- Infection
- Trauma?
- Is it really hemorrhagic conversion – how do we tell?

Blood pressure?

- MAP > 90 with HVAD (Najjar, JHLT 2014)
- Not on antihypertensives a risk factor for stroke (Lampert, Ann Thor Surg 2014)
- Makes sense: consistent risk factor for stroke in the general stroke population (Go, Circulation 2014)
- BP on discharge associated with subsequent stroke (Nassif, JHLT 2015) - > median 48hrs prior to d/c
- High DopplerBP associated with ICH, not ischemic stroke, and also worsening baseline renal function (Saeed, Circ Heart Fail 2015)

Hemorrhagic stroke

- ICH and hemorrhagic conversion are not well differentiated
- Rates of both are higher in the CF-LVAD population and not explained by coagulopathy, acquired vonWillebrand's disease, or renal failure
- Hypertension levels not typical for what conveys risk of stroke
- Hemorrhagic conversion present at onset

Cerebral endothelial dysfunction

- Study of exercise induced TCD (Cornwell, JHLT 2014) showed no impairment by device type
  - Limitations of testing paradigm
  - Follow up showed restoration of sympathetic nervous system activation with return of pulsatility (Cornwell, Circulation 2015)
- Other studies on cerebral endothelium are lacking, including in animal models

Stroke in ECMO

- Mayo clinic case series (Mateen, Arch Neurol 2011)
  - All patients had antecedent cardiac surgery or event
  - 87 adults, mean ECMO 91 hrs , 14 post arrest
  - Neuro events in 42 pts. Dx = SAH, ischemic stroke, HIE, coma, and brain death
  - < 50% of those with neuro events survived
  - Predictors: age and nadir oxygen

Stroke in ECMO

- Mechanisms of stroke may be due to type of ECMO used and indications
  - ICH may be more common, especially in neo-nates and when used for cardiac disease (Harvery-Jumper, J Neurosurg Pediatr 2011)
  - Severity of initial disease
  - Changes in CBF (O'Brien, Pediatr Crit Care Med 2013)
  - Air emboli and cerebral microbleeds (Liebeskind, J Neuroimag 2013)
  - Thrombotic events