

Delirium, anesthesia, and the
manipulation/management of
perioperative stress

Stacie Deiner M.D. M.S.

Associate Professor of Anesthesiology,
Neurosurgery, Geriatrics and Palliative Care
The Icahn School of Medicine at Mt. Sinai

Disclosures

- Current funding: Jahnigen Scholar Program
American Geriatrics Society, NIA GEMSSTAR R03
- Previous: Mt. Sinai Alzheimer's Disease
Research Center Pilot Program

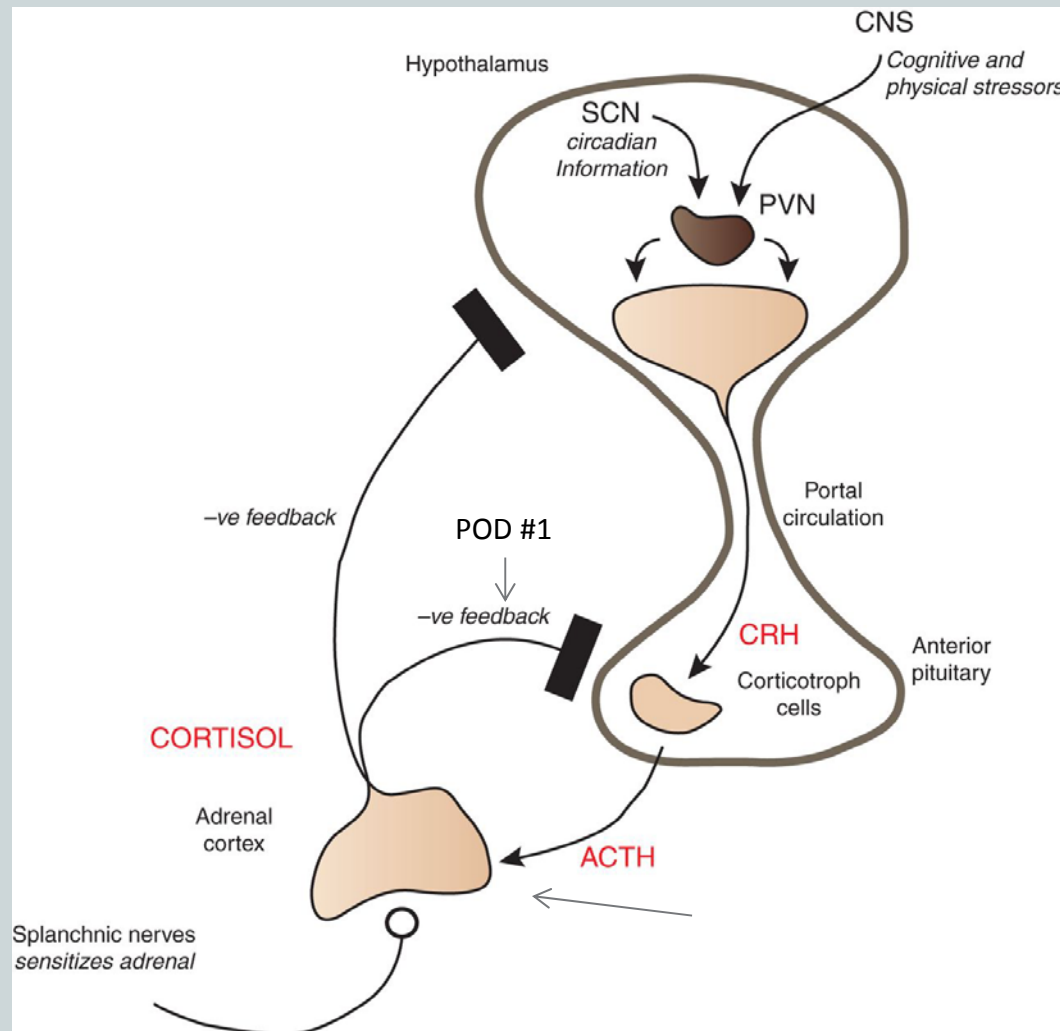
Other financial relationships: None

Conflicts of interest: None

Purpose

- Describe the stress response to surgery
- Discuss the effect of anesthesia on the stress response
 - Is postoperative delirium related to the neuroendocrine stress response to surgery?
 - Is it possible to reduce the incidence of delirium through anesthetic choice?

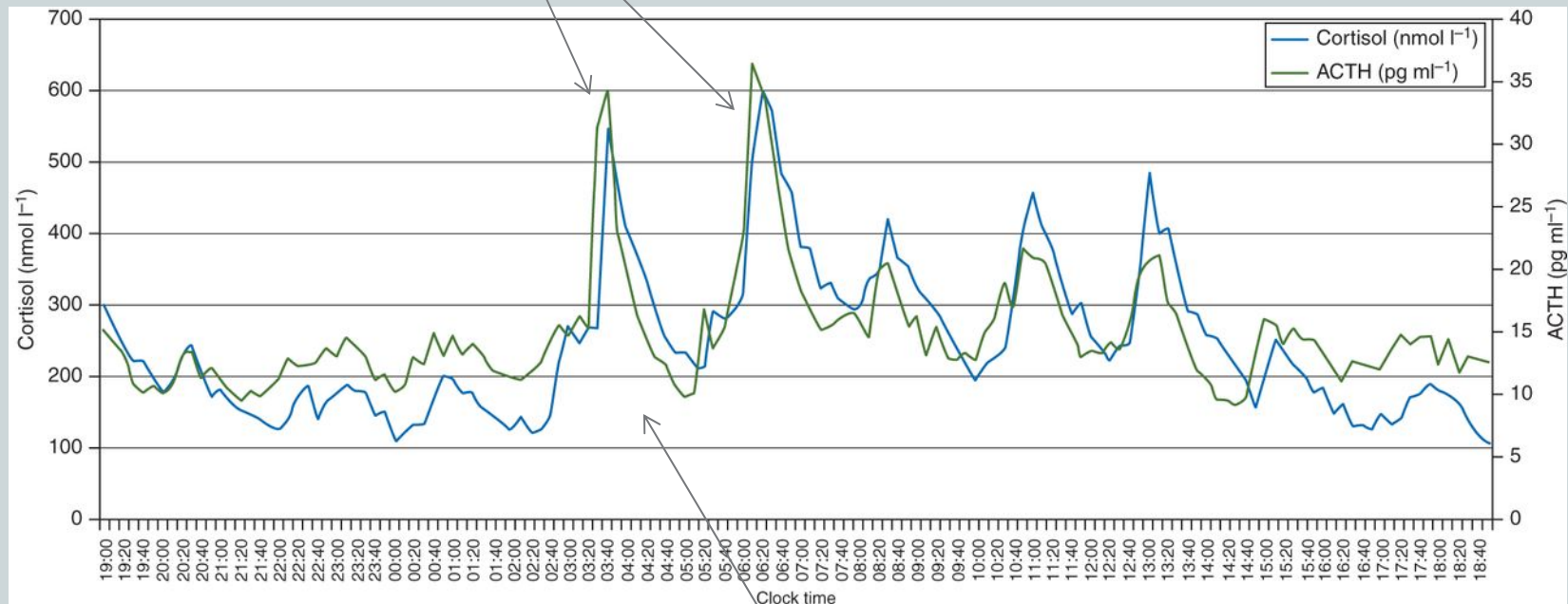
Hypothalamic-Pituitary Adrenal Axis Control



Gibbison B et al. Br. J. Anaesth. 2013;111:347-360

A normal ultradian rhythm of both cortisol (blue) and ACTH (green)

Stressors during the rising phase can result in different outcomes: exaggerated response during the rising phase, relative refractory during the falling phase

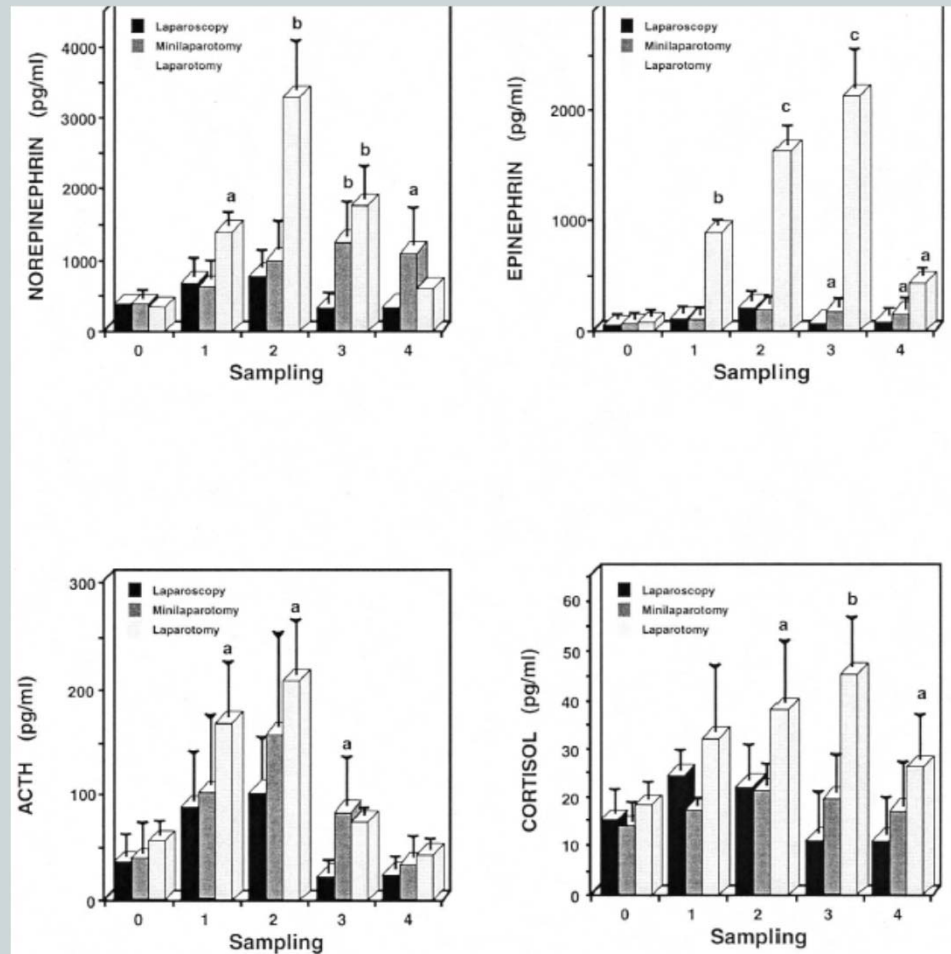


Gibbson B et al. Br. J. Anaesth. 2013;111:347-360

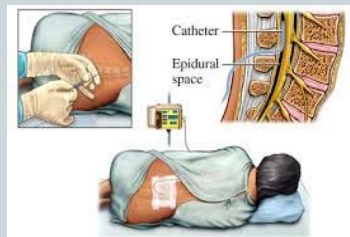
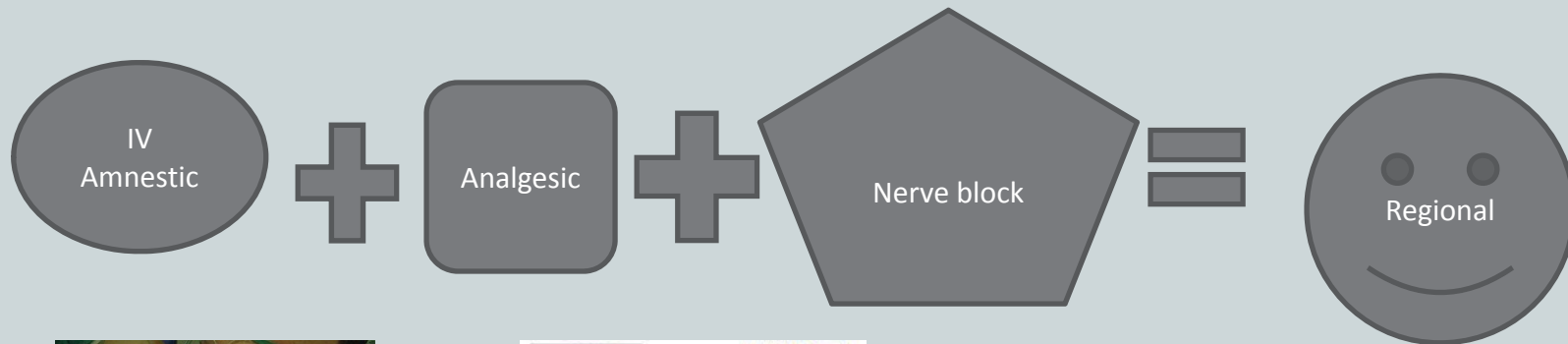
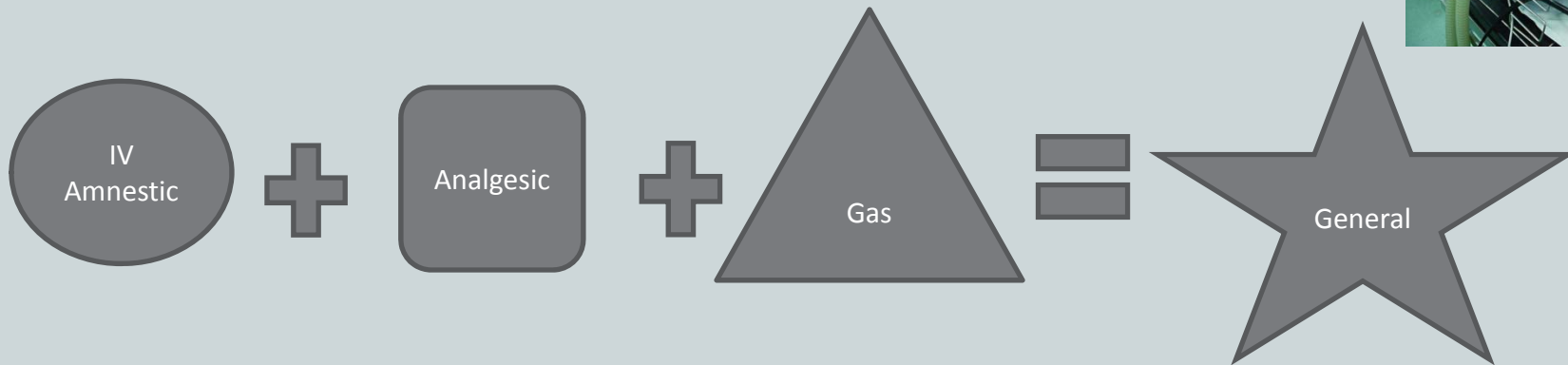
Stress and surgery/anesthesia

- Begins with anxiety
- Salivary cortisol increases 50% after preoperative information session
- Increases with pain and inflammation
- Magnitude varies by surgery and anesthetic type

Stress Response: laparoscopic vs. minilap vs. laparotomy

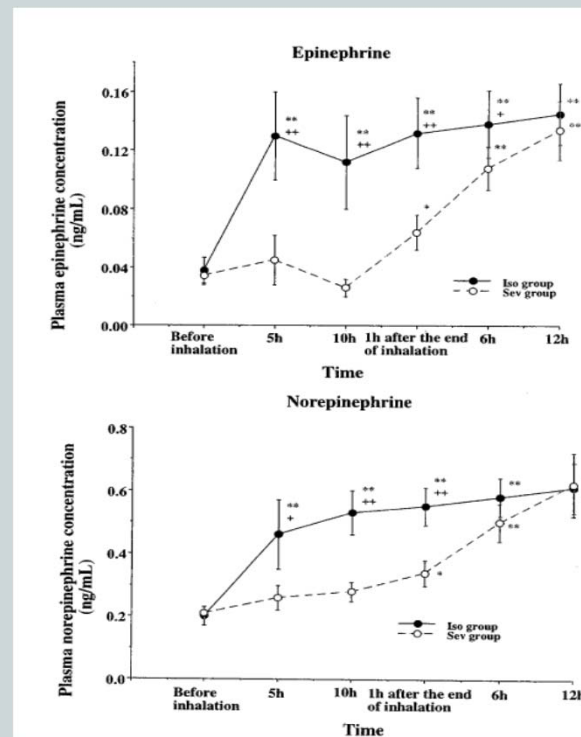
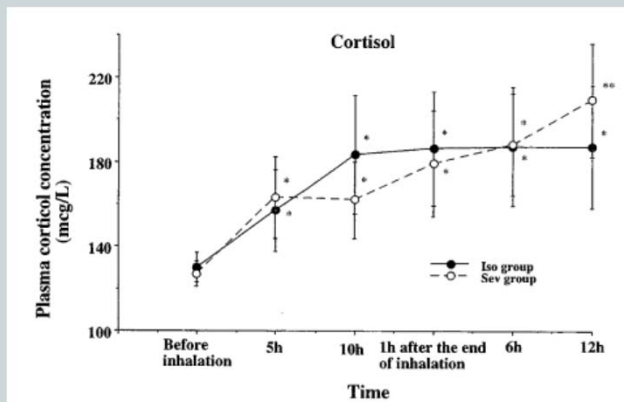


Anesthesia is a cocktail

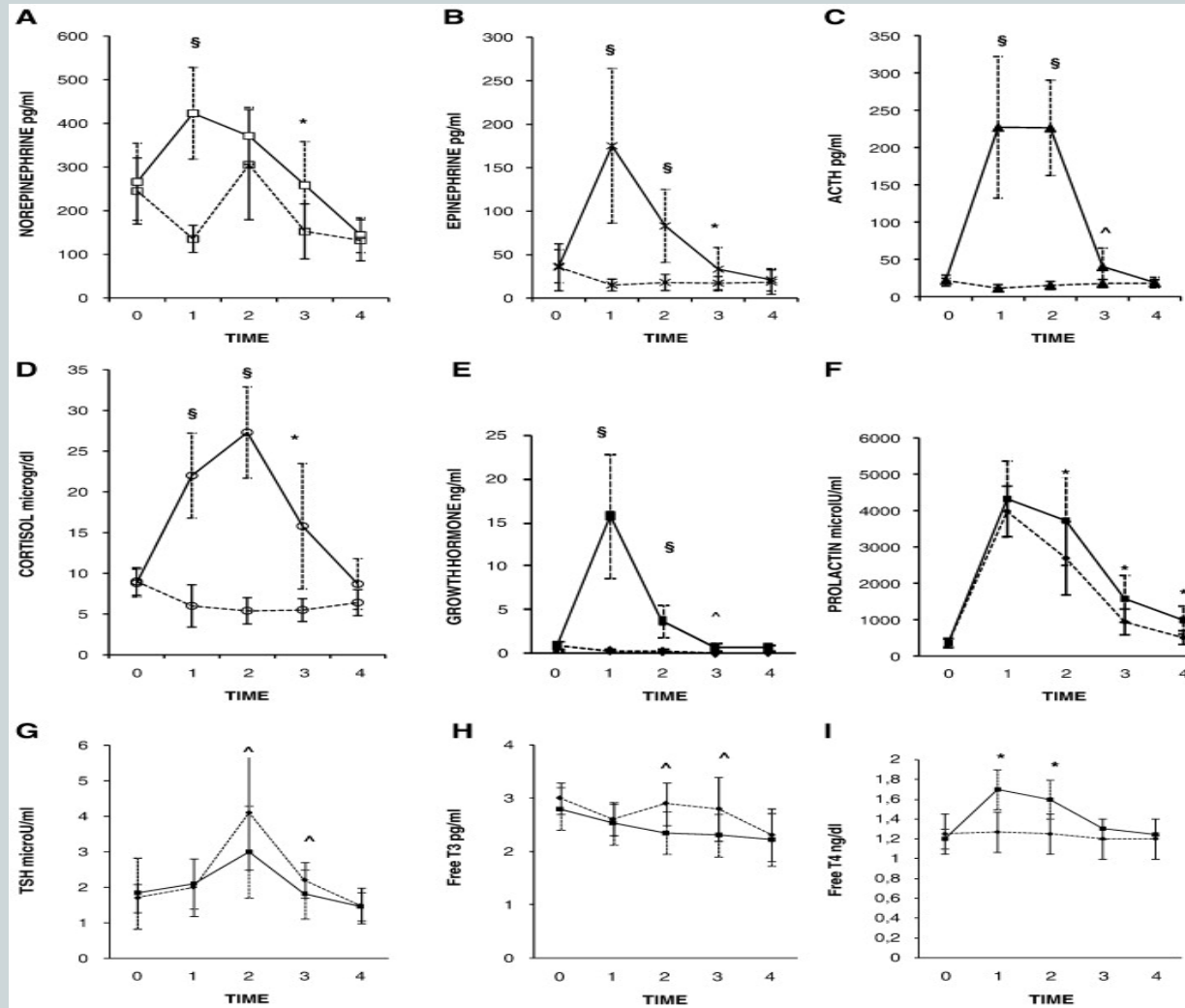


Stress response and anesthetic gases

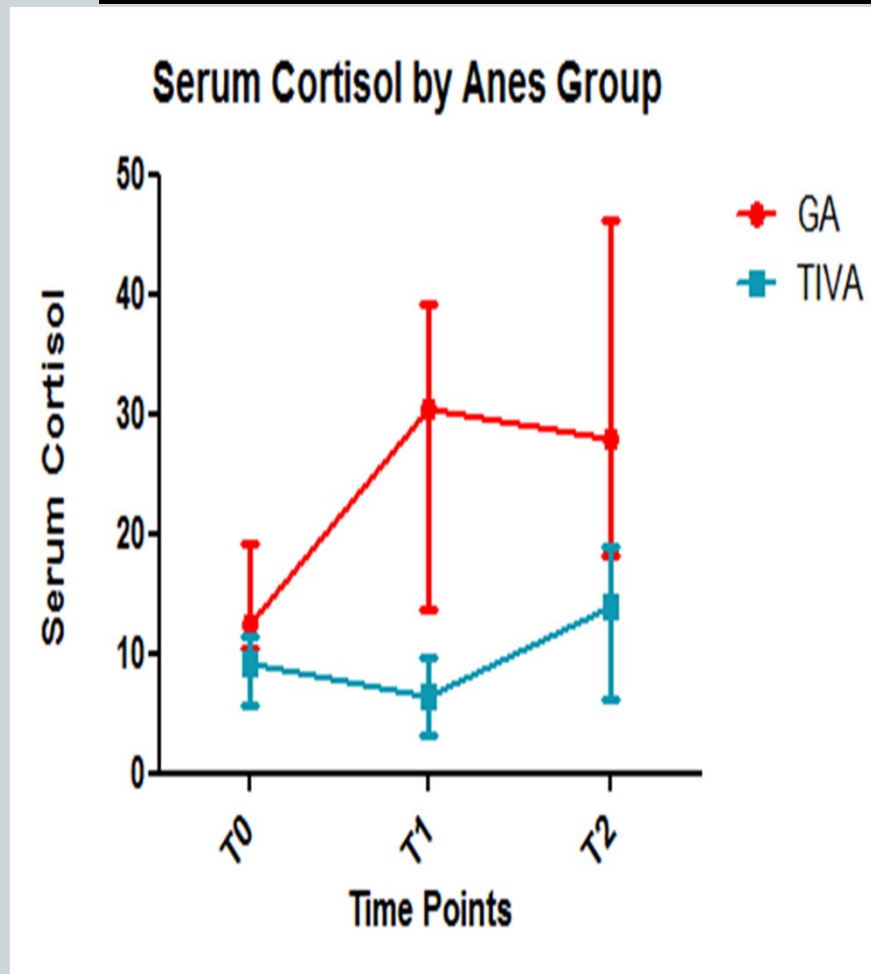
- minimally suppress cortisol response
- Some gases suppress catecholamines more than others



IV Anesthetics : propofol vs. gas



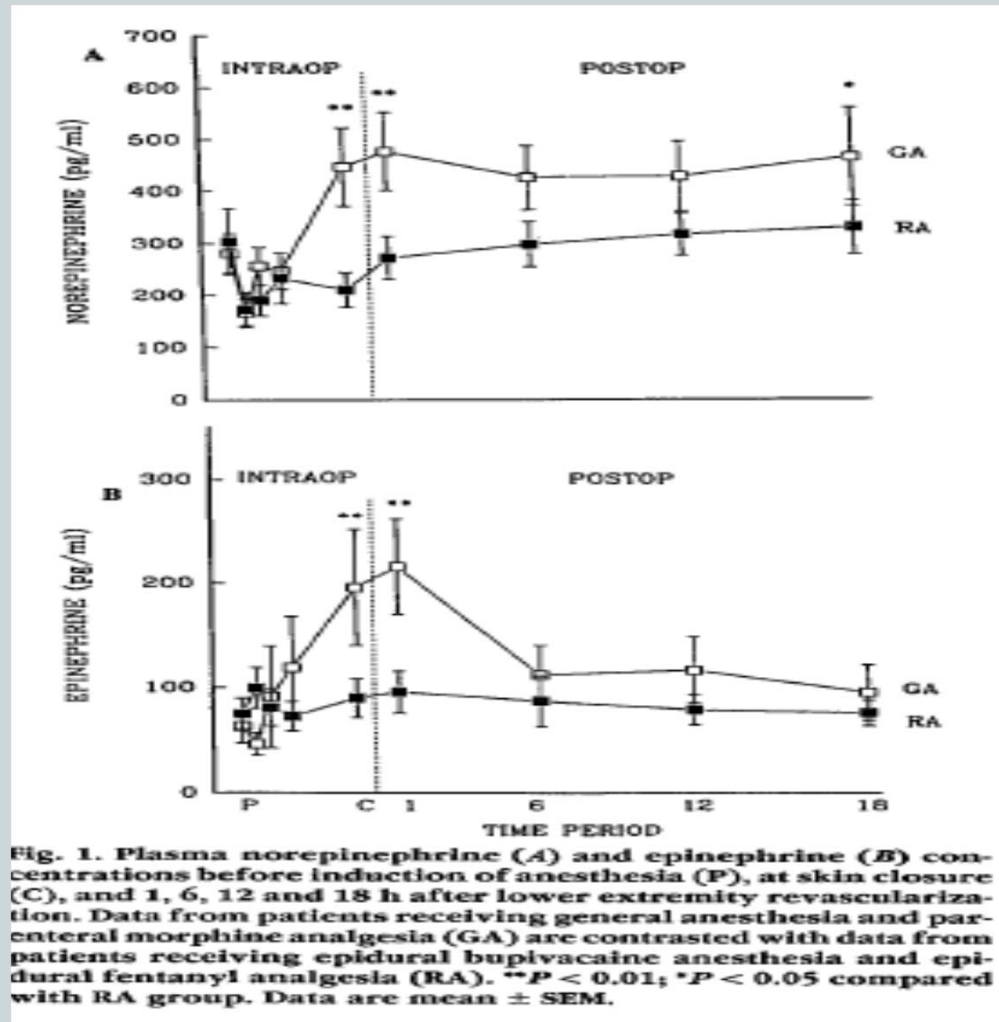
Robust phenomenon in the elderly: serum cortisol by anesthetic



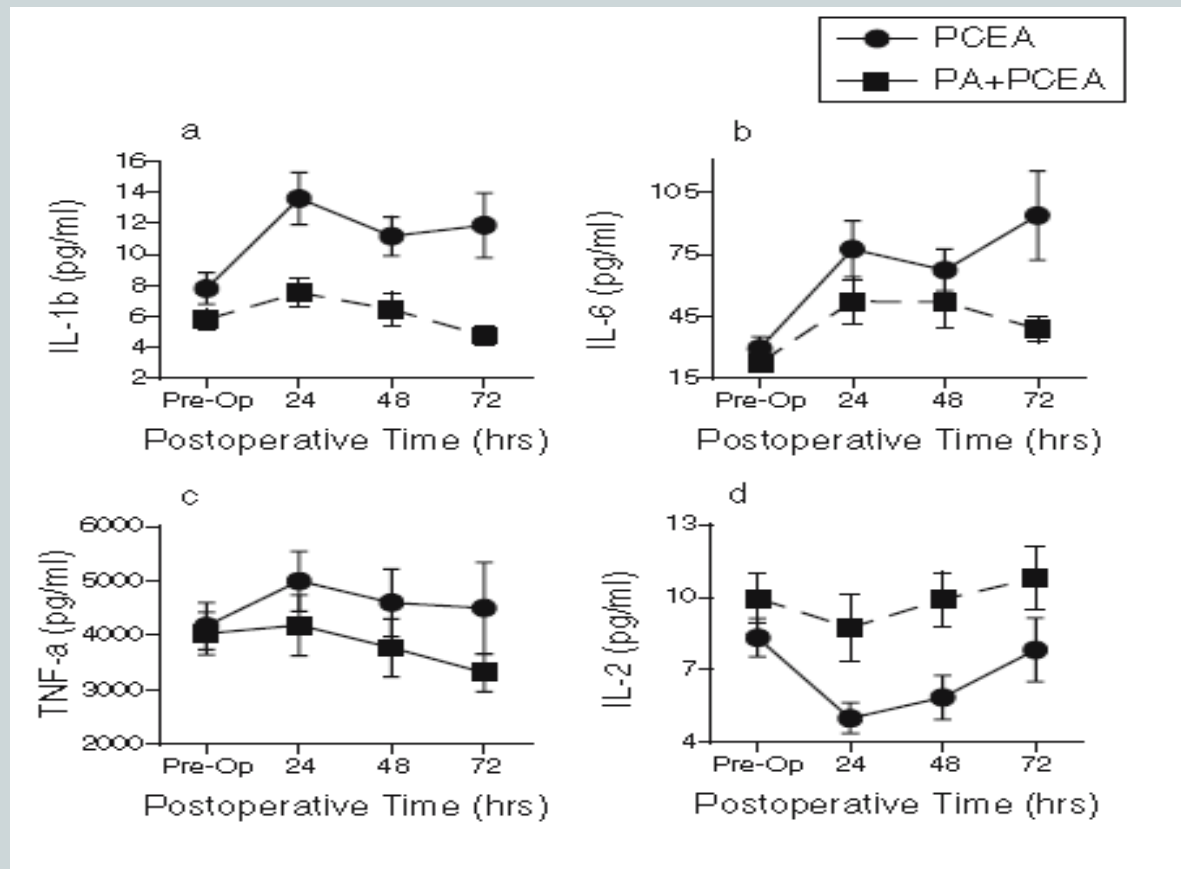
N=56

Deiner S., Abstract, AGS 2013

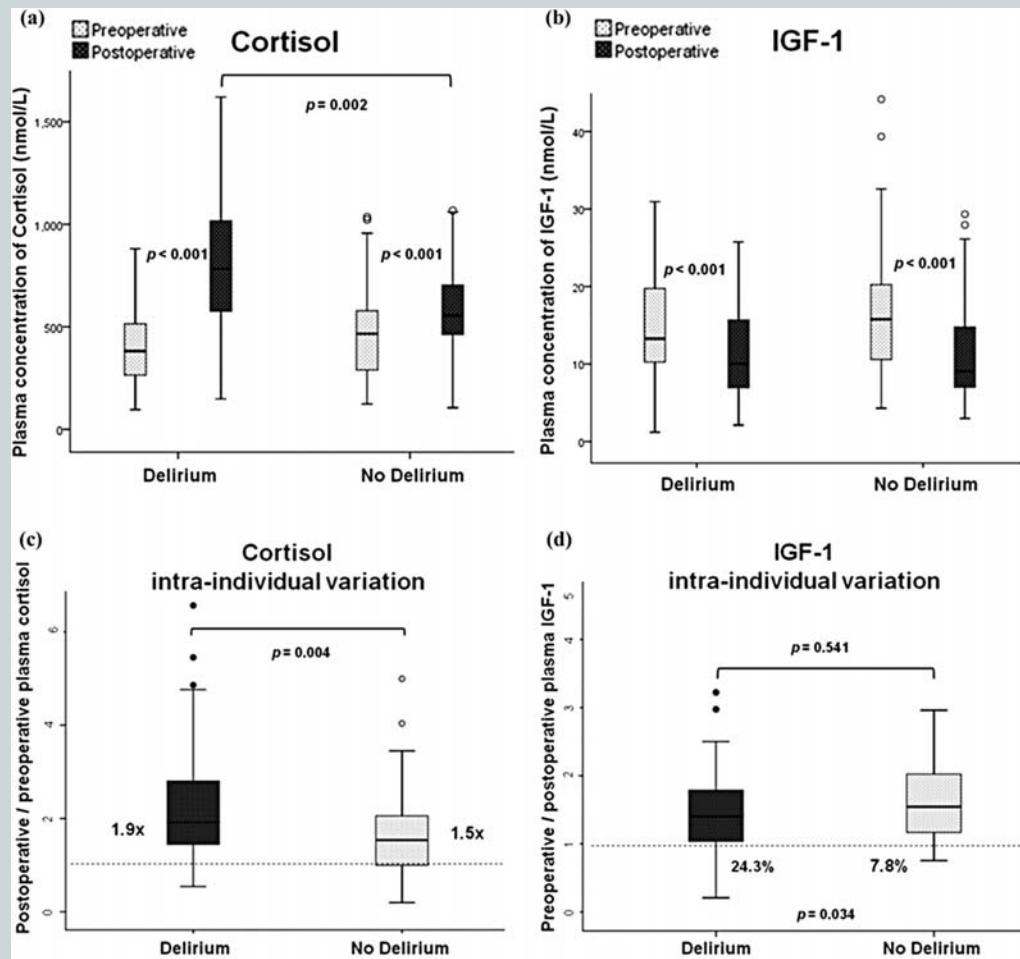
Neuraxial anesthesia vs. general anesthesia and catecholamines



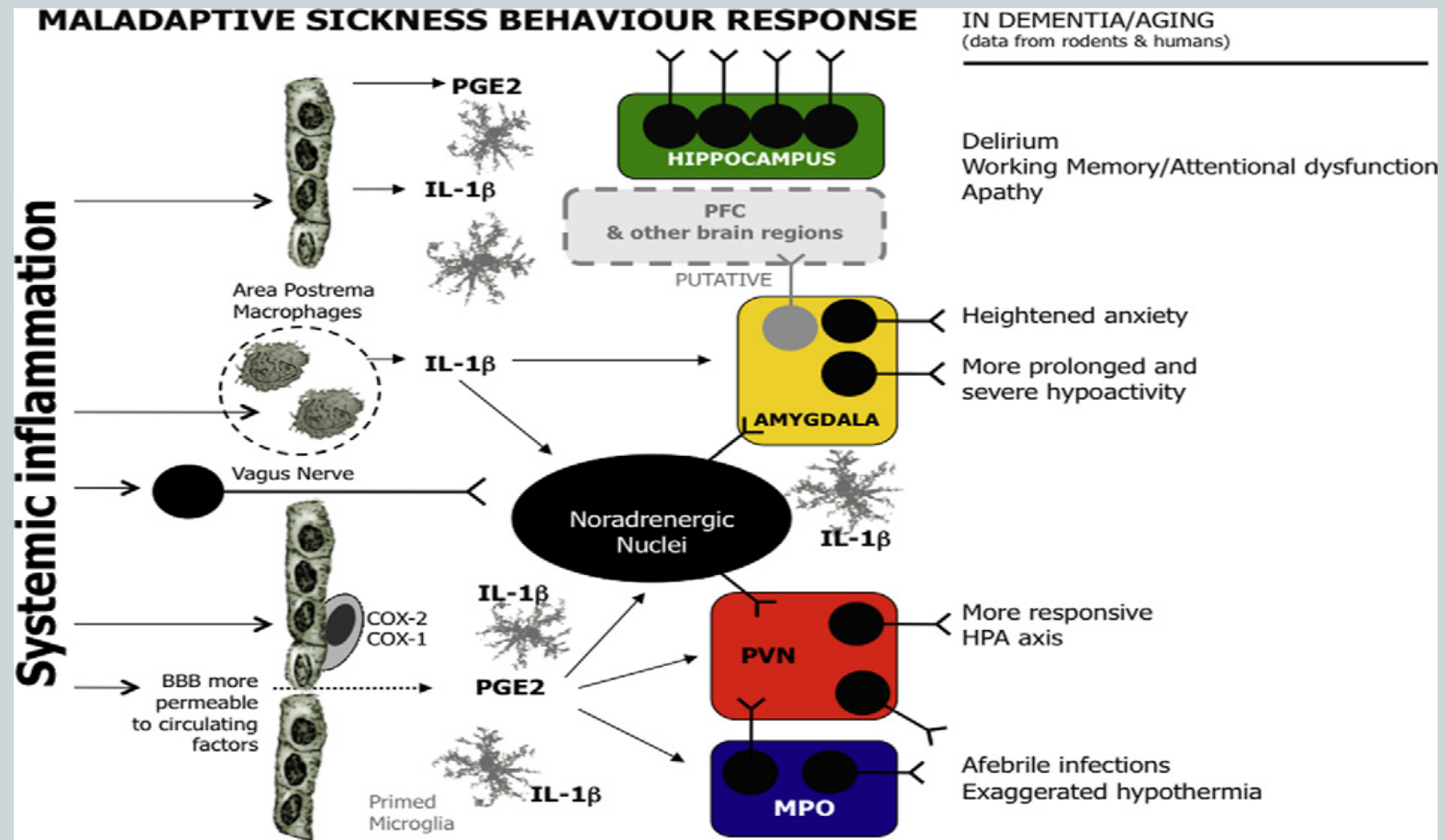
Combination general anesthesia plus epidural



Connection between stress response and delirium



Mechanism behind the stress response and delirium



Cunningham et al Brain, Behavior, and Immunity 2013

Delirium and anesthesia

- Zhang metaanalysis
 - review of RCTs prior to August 2012
 - 198 articles – 38 RCTs
- Inconsistence in definition of delirium
 - Use of a variety of measures
 - DSM, CAM, DRS, NEECHAM Confusion Scale
- Issue- different types of surgery

**38 articles included**

- 1 controlled hypotension (marked vs. mild)**
- 9 anesthesia:**
 - 4 neuroaxial anesthesia (NA) vs. general anesthesia (GA) ***
 - 4 anesthetics**
 - 1 depth of sedation during spinal anesthesia**
- 5 postoperative analgesia**
 - 3 epidural analgesia vs. intravenous analgesia ***
 - 1 additional fascia iliaca compartment block vs. standard analgesia**
 - 1 morphine vs. placebo**
- 3 postoperative sedation (alpha-2 adrenergic receptor agonists vs. standard) ***
 - 2 dexmedetomidine vs. routine sedatives ***
 - 1 additional clonidine vs. routine sedatives**
- 4 acetylcholinesterase inhibitors vs. placebo ***
- 6 antipsychotics vs. placebo ***
 - 3 typical antipsychotics (haloperidol) vs. placebo ***
 - 3 atypical antipsychotics (olanzapine or risperidone) vs. placebo ***
- 2 anticonvulsants (gabapentin or pregabalin) vs. placebo ***
- 1 sleep restoration using diazepam/flunitrazepam/pethidine vs. standard**
- 2 sleep restoration using bright light vs. standard ***
- 1 psychological intervention vs. standard**
- 1 music vs. standard**
- 2 multicomponent intervention vs. standard ***
- 1 histamine H₂ receptor blockers (cimetidine vs. ranitidine)**

Studies comparing delirium between different types of general anesthesia

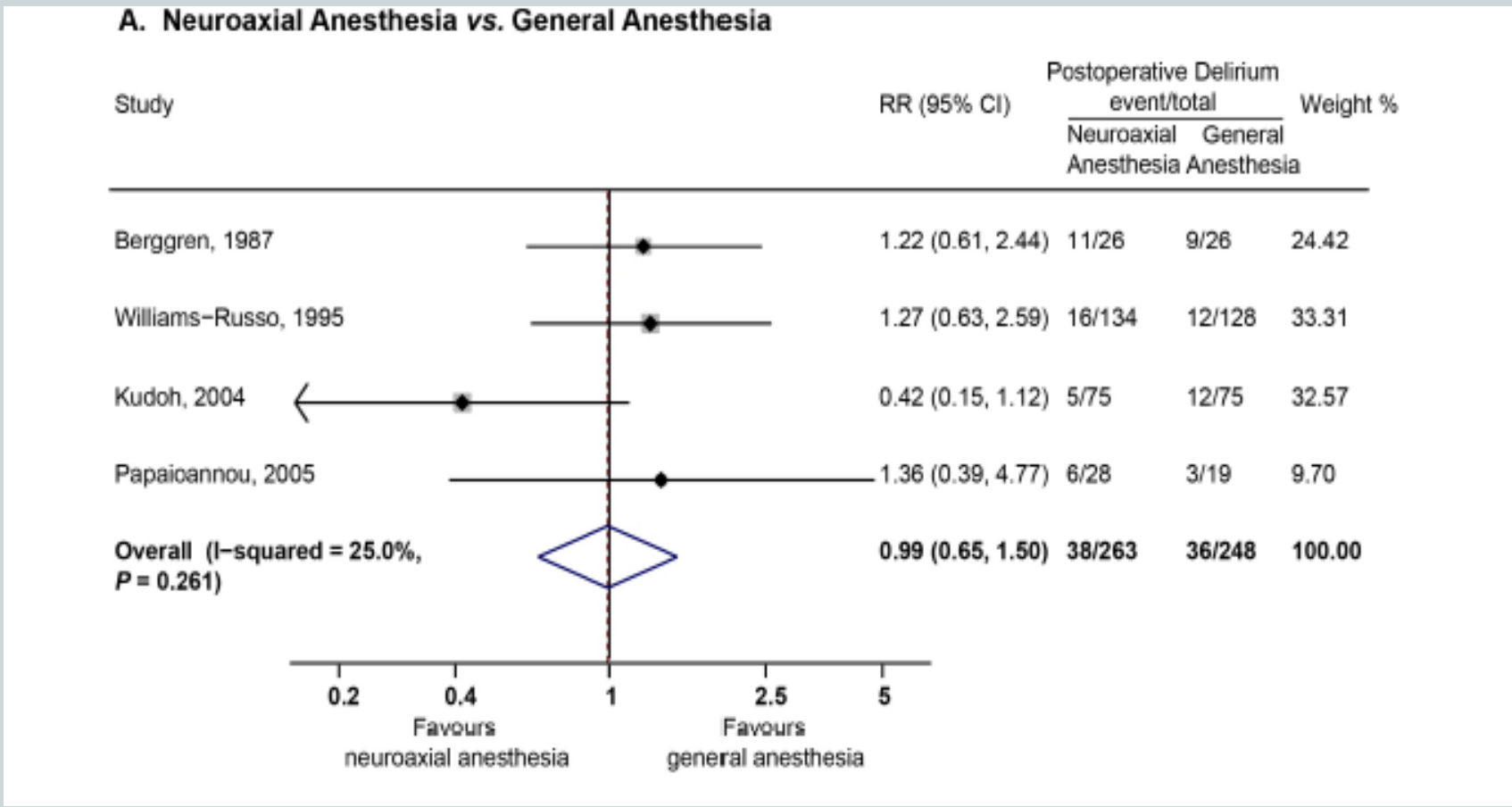
- Comparison of 2 general anesthetics: gas vs. total intravenous anesthesia
- Mixed results
 - Nishikawa et al 2004: higher DRS and trend toward increased incidence for propofol (16%) vs. sevoflurane (0%) (but NS)
 - Monk et al 2011 propofol vs. isoflurane in major ortho surgery no difference (12.6% vs. 13.6%)
 - Royse et al 2011 propofol vs. desflurane in cardiac surgery - no difference (7.9% vs. 13.2%)

Delirium and neuraxial vs. general anesthesia

Neuraxial= epidural or spinal

- 4 Randomized controlled trials
- Each study used a different maintenance anesthetic
- halothane, isoflurane, propofol

Pooled RR of POD = .99 CI .65 to 1.5
 Incidence approximately 17%



Deiner 2013 AGS Abstract 2013

- Study design: Prospective cohort study
- Subjects: >68 years old for major elective noncardiac surgery. Identified by the computerized scheduling system at Mount Sinai Hospital
- Outcomes: Delirium, POCD, postoperative complications
 - Measured at screen, 3 and 6 months.
- Predictors:
 - Primary: anesthetics technique (GS vs. TIVA),
 - Secondary: serum norepineprine,epinephrine, cortisol

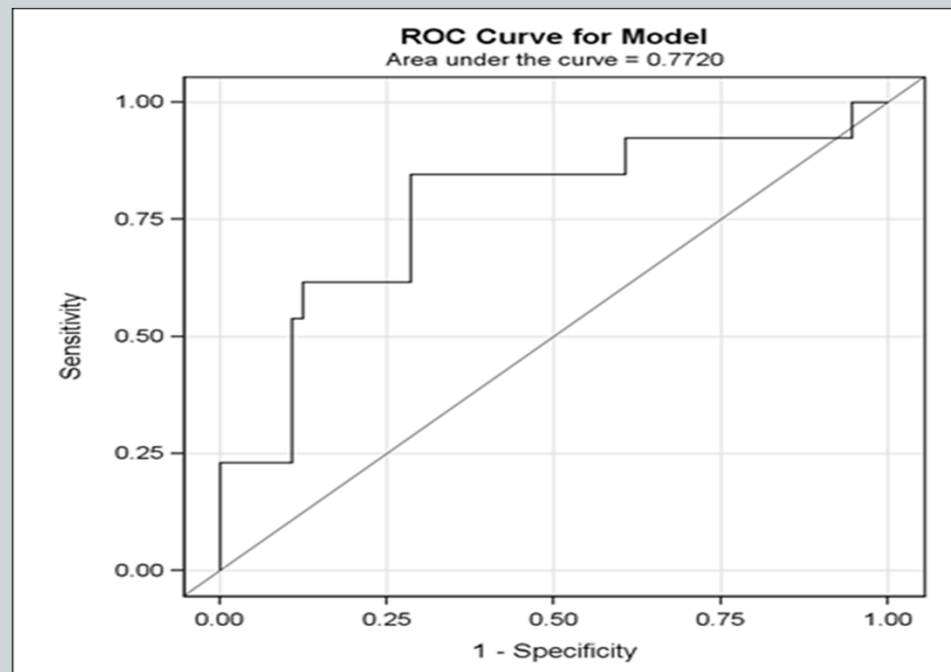
Cont'

- Delirium was not different in the PACU (Gas 3.2% vs. TIVA 8.1% $p = .62$)
- Opposite trend in the postoperative period (Gas 19.4% vs. TIVA 12.5% $p = .41$).
 - 30% reduction, but would have needed 476/arm for significance
 - Consistent with Royce's findings

Model to Predict Delirium: diabetes, serum norepinephrine, surgical duration



Predictor	Unit	Odds Ratio	95% CI
Surgical Duration	1 hour	1.46	0.92-2.32
Norepi Time 2	100 pg/ml	1.20	1.01-1.42
Diabetes	1= yes	4.51	1.01-20.14



Deiner et al,

Confounding issues

- Pain
 - Treatment of pain
- Hypothermia, shivering
- Depth of anesthesia
 - Sedation given with regional anesthesia
- Adjuvant agents may not be inert: steroids, ketamine
- Immediate postoperative delirium= inadequate emergence?

Conclusion

- Do anesthetics suppress the stress response to surgery (yes, some more than others)
- Is delirium related to stress? (likely)
- Is it possible to reduce the incidence of delirium through anesthetic choice (maybe)

Thank you

NIA GEMSSTAR R03

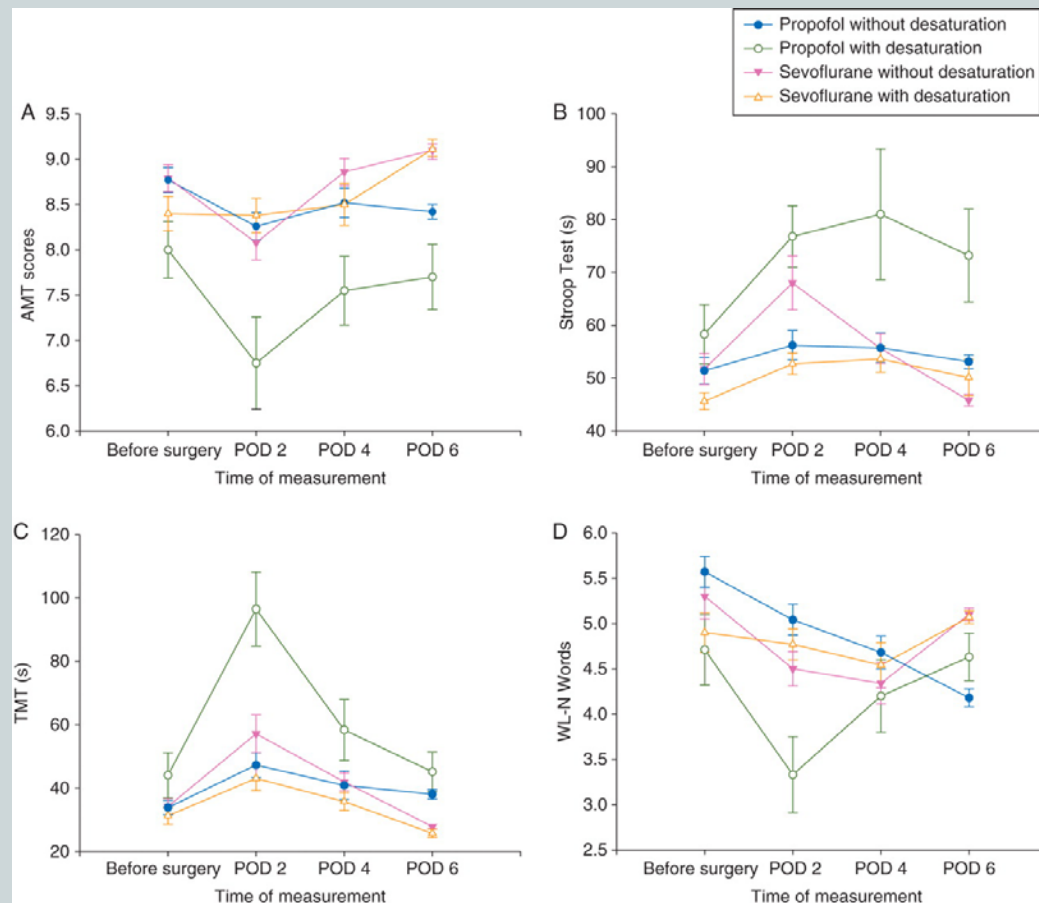
American Geriatrics Society Jahnigen Program

Alzheimer's Disease Research Center

Icahn School of Medicine at Mount Sinai Research Staff



Results of the cognitive tests in patients after a sevoflurane- or propofol-based anaesthesia during on-pump cardiac surgery in patients with and without cerebral desaturation.



Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision--MAC BAR

TABLE 5. Comparison of MAC with MAC EI and MAC BAR*

	MAC ₅₀ †	MAC ₉₅	MAC EI ₅₀ ^{26,27‡}	MAC EI ₉₅ ^{26,27}	MAC BAR ₅₀ §	MAC BAR ₉₅
Halothane	1.0 MAC 0.74 ± 0.03 per cent	1.2 MAC	1.3 MAC	1.7 MAC	1.5 ± 0.1 MAC	2.1 MAC
Enflurane	1.0 MAC 1.68 ± 0.04 per cent	1.1 MAC	1.4 MAC	1.9 MAC	1.6 ± 0.1 MAC	2.6 MAC
Morphine sulfate	—	—	—	—	1.13 ± 0.1 mg/kg plus 60 per cent N ₂ O	1.5 mg/kg plus 60 per cent N ₂ O

“If adverse effects of surgery are related to the neuroendocrine stress that surgical manipulations induce, the hypothesis the less anesthetic the better may be wrong.”

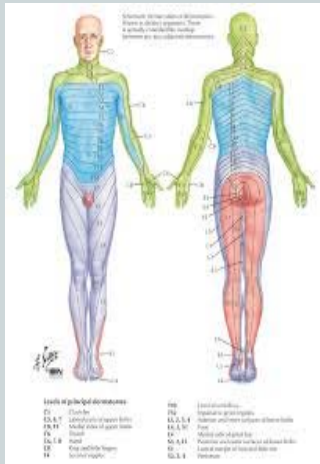
Roizen et al Anesthesiology 1981

Spinal (regional anesthesia) blocks the adrenergic response to incision

TABLE 4. Preincision Plasma Norepinephrine Concentrations

	Age-adjusted MAC Level	Preincision Plasma Norepinephrine Concentration (pg/ml)*
Enflurane plus 60 per cent N ₂ O	1.3 MAC	292 ± 117
	1.6 MAC	282 ± 171
	1.9 MAC	360 ± 172
Halothane plus 60 per cent N ₂ O	1.0 MAC	415 ± 186
	1.3 MAC	393 ± 276
	1.6 MAC	441 ± 247
	1.9 MAC	515 ± 310
Morphine plus 60 per cent N ₂ O	0.4 mg/kg	308 ± 200
	0.9 mg/kg	330 ± 139
	1.4 mg/kg	324 ± 100
Spinal anesthesia	T10 level	255 ± 150
	T4 level	235 ± 135

* Values are means ± SD.



Roizen et al Anesthesiology 1981