# Postoperative Cognitive Dysfunction

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# Postoperative Cognitive Dysfunction

- Concept triggered by Bedford's 1955 report in Lancet "Adverse cerebral effects of anesthesia in old people"

- No postoperative complication more prevalent or of longer duration than POCD in the elderly population

# Why is this important??

- 2nd Duke University Conference on Surgery and the Elderly (September 1999)
- The incidence of major complications, including death, is significantly higher in patients who have POCD. (Ronnie Rosenthal, Yale University)
- After cardiac surgery: cognitive dysfunction affected > 50% of patients at discharge
  - incidence fell to 20-24% at six months
  - Increased to 42% at five years
  - **Most significant predictor at 5 years was impairment at discharge

# Geriatric statistics

- Every 8 seconds a baby boomer turns 60.
- “By 2012, nearly 15% of our population will be over 65 years of age”
- 1999: 40% of surgeries were performed on patients over the age of 65
- Elderly population is increasing; therefore, the number of elderly patients having surgery is increasing

# Why is this important??

- International Study of Postoperative Cognitive Dysfunction 1 (ISPOCD1)– 1988
- POCD occurred in 25% of patients in 1st week following surgery
- 10% within 3 months of surgery
- Patients >70 years of age were more susceptible to prolonged POCD
- **Study convincingly established the existence and prevalence of POCD as a defined clinical entity in elderly patients

# Definitions

- ***Cognition***
  - Mental processes of perception, memory, and information processing
    - Allows for acquiring knowledge, solving problems, planning for the future
    - Comprises mental processes needed for everyday living – not intelligence
- ***Delirium***
  - Hallmark signs are disorientation, attention deficits, clouding of consciousness
  - Develops over a short period of time (hours or days)
  - Degree of severity ranges from mild to very severe

# Definitions

- ***Short-term cognitive dysfunction***
  - Relatively frequent
  - Does not persist beyond a few days after surgery
  - Transitory and does not represent a long lasting condition
- ***True POCD***
  - Subtle deterioration in cognitive function
    - Lasts for weeks, months, or longer
  - Can be considered a mild disorder characterized by memory impairment, learning difficulties and reduced ability to concentrate
  - Neuropsychological testing is needed for verification

# Definitions

- ***Dementia***
  - Due to a disease of the brain
  - Chronic or progressive in nature
  - Disturbance of multiple higher cortical functions
    - Memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment
  - Consciousness is not clouded
  - Can be accompanied or preceded by deterioration in emotional control, social behavior, or motivation
  - Demented patients can pay attention but cannot remember

# Is there an increased risk for Alzheimer's Disease patients?

- Avidan et al (2009)
  - Study did not detect long-term POCD attributable to surgery or illness
  - Nearly ¼ of nondemented participants progressed to very mild or mild dementia; however, risk of progression was not greater in the surgery or illness group
- Gasparini et al (2002)
  - No difference between AD cases and controls regarding any general anesthetic exposure in 1-5 years preceding onset

# Stroop Color Word Interference Test

## Green

| | | | | |
|---|---|---|---|---|
| RED | GREEN | BLUE | YELLOW | PINK |
| ORANGE | BLUE | GREEN | BLUE | WHITE |
| GREEN | YELLOW | ORANGE | BLUE | WHITE |
| BROWN | RED | BLUE | YELLOW | GREEN |
| PINK | YELLOW | GREEN | BLUE | RED |

www.faculty.washington.edu/chudler/java/ready.html

# Visual Verbal Learning Test

- Rey Auditory Verbal Learning Test
  - Originally developed in 1940s
  - Used to evaluate verbal learning and memory in patients from 7-89 years of age
- List of 15 words read aloud
  - Rate of one word/1-2 seconds
- Test-taker's task is to remember as many words as possible, in any order

# Risk factors for POCD

- Increasing age
- History of CVA with no residual impairment
- Years of education
- Duration of anesthesia
- Surgical complications
- POCD at discharge
  - Higher ASA physical status
  - More complicated surgery
  - Longer hospital stay

# Proposed mechanisms of POCD

- Exposure to volatile anesthetics?
  - Linking exposure to the generation of amyloid or direct neurotoxicity
    - Propofol does not have same effect
  - Direct neurotoxic effects
- Hormonal effects
  - Hypothalamic-pituitary-adrenal hormones
  - Sympathetic nervous system hormones

# Proposed mechanisms of POCD

- Inflammatory mediators
  - Cytokines
- Slow elimination of CNS-active drugs used during and after the anesthetic
- Sleep deprivation
- Postoperative pain
- Disorienting effect of strange environment

# Major limitations of research studies

- Newman et al (Anesthesiology 2007) *Postoperative Cognitive Dysfunction after Noncardiac Surgery: A Systematic Review*
  - Number and time of assessments
  - Assessment and definition
  - Number of tests used
  - Learning between tests
  - Attrition due to death, refusal, lost to follow-up

# The art of Evidence Based Decision Making

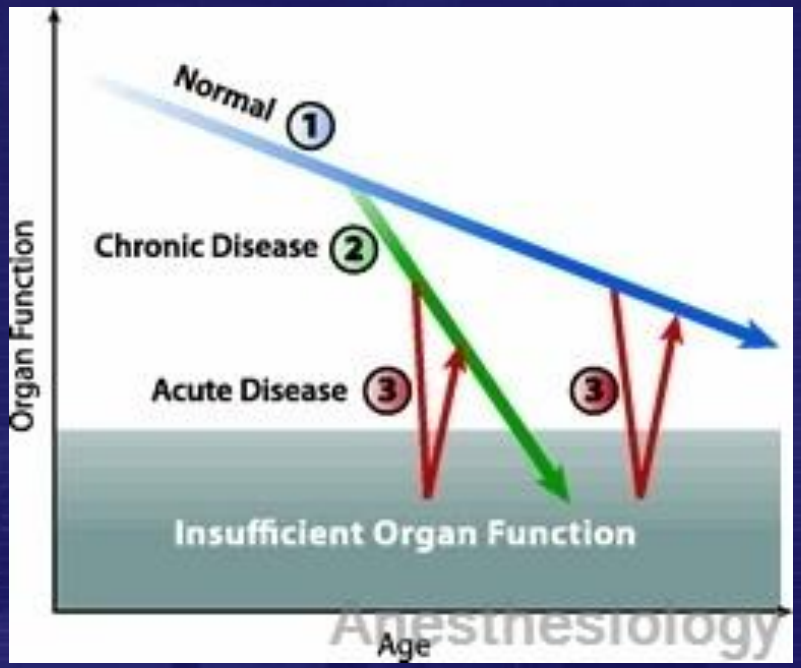
- “Evidence base practice (EBP) is. . . the marriage of excellent clinical science. . . by extracting the contextually essential, best information from the vast, representative research literature and merging it with the art of applying it to a patient is EBP at its finest.”
  - Chuck Biddle, CRNA, PhD Evidence Trumps Belief. 2010. American Association of Nurse Anesthetists

# Perioperative drug therapy between the generations

- Advances in modern medicine and public health have resulted in increased longevity
  - More elderly patients in surgery (arbitrarily defined as age 65 yr or older)
  - ↑ in comorbidities
  - Respond differently to pharmacologic interventions

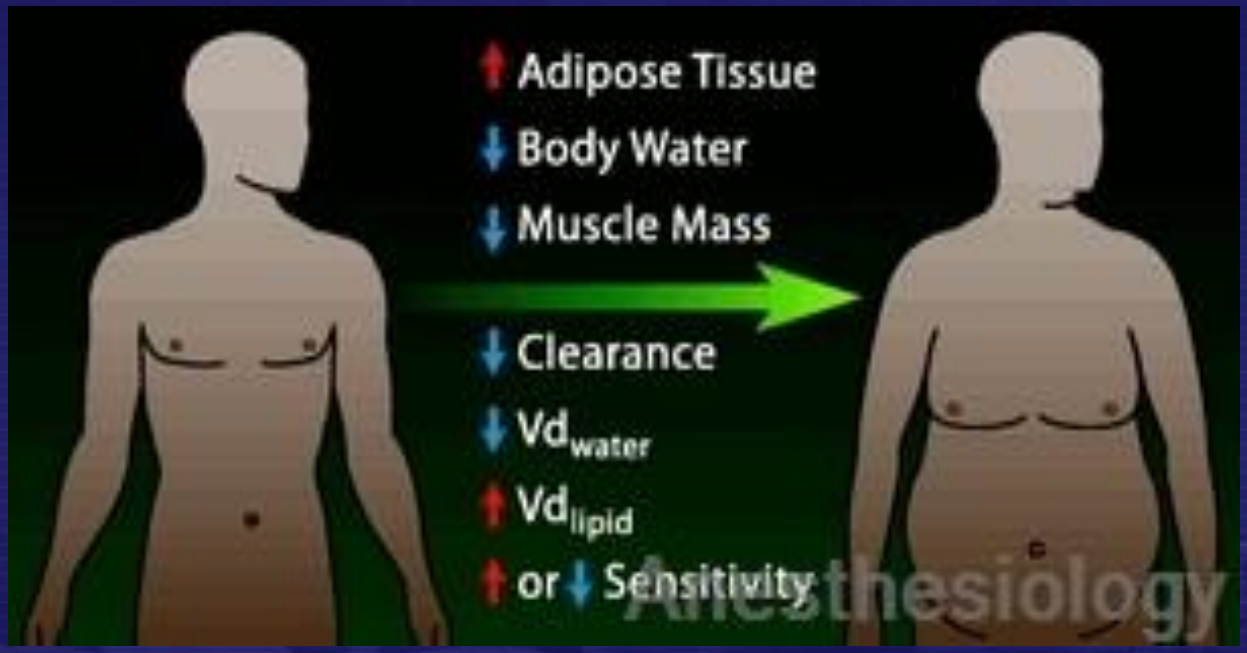
**WHY??**

# Perioperative Drug Therapy in Elderly Patients Organ Function




Rivera, Richard; Antognini, Joseph F.
Anesthesiology. 110(5):1176-1181, May 2009.

# Pharmacokinetics




Rivera, Richard; Antognini, Joseph F. Anesthesiology. 110(5):1176-1181, May 2009.

# Perioperative drug therapy in the elderly

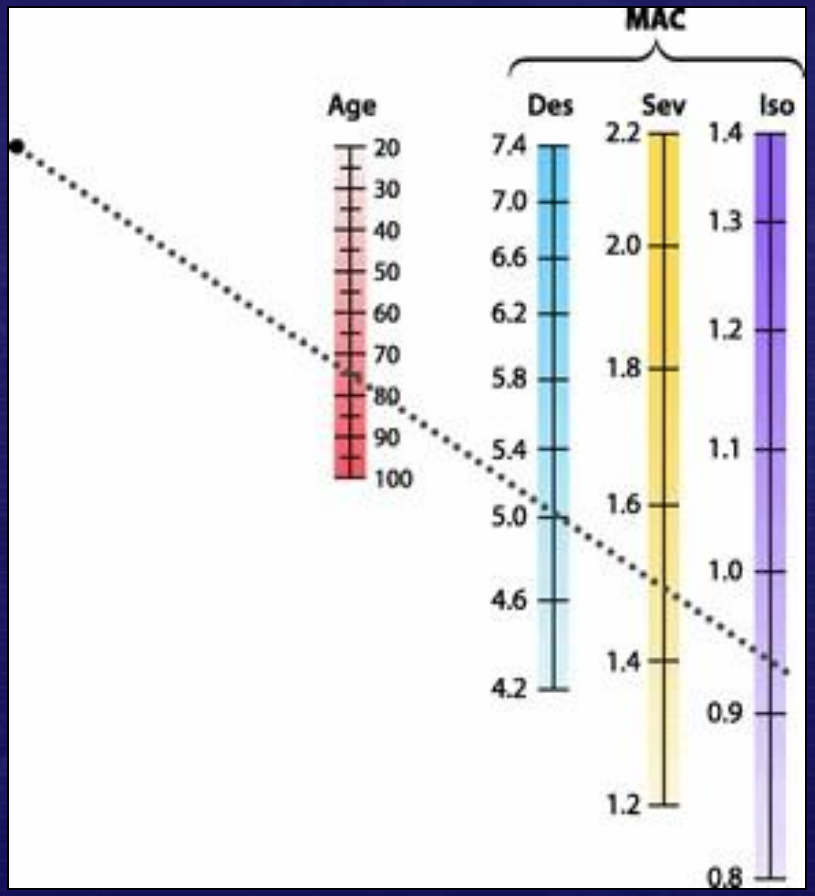
## Pharmacokinetics

- ↑ Volume of distribution of lipid soluble drugs
- ↓ protein binding
- ↓size and blood flow to liver
- Clearance *by* and blood flow *to* liver ↓ 30-40%
  - ↓ Liver metabolism
- ↓ renal elimination from advancing glomerulosclerosis

## Pharmacodynamics

- Alterations in the number of receptors at the target site and signal transduction (response to receptor stimulation) may be altered
- Little research done in the geriatric population
- Elderly or *more* or *less* sensitive to drugs
  - *More* to benzodiazepines and propofol
  - *Less* to β blockers

# MAC levels decline with age




Rivera, Richard; Antognini, Joseph F. Anesthesiology. 110(5):1176-1181, May 2009.

# MAC levels

- MAC and MAC awake levels decline 0.6% for each year over 40 years of age
  - Age affects the nervous system through altered synaptic or neuronal function (pre and post synapse)
  - Dopaminergic and cholinergic neurotransmitters altered through free-radical formation
  - Cerebral atrophy

# Induction agents, opioids, and muscle relaxants

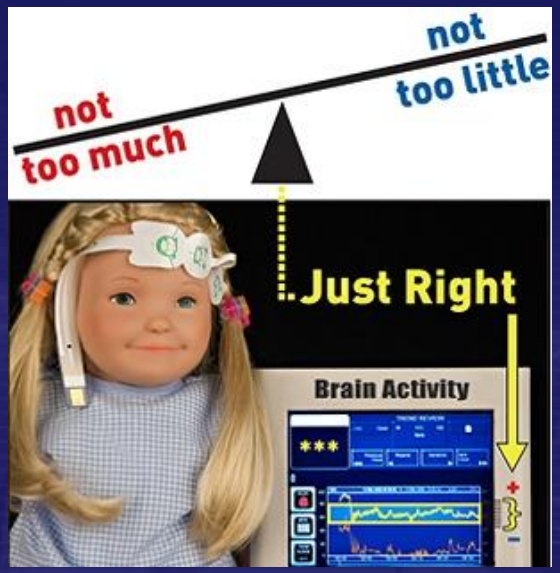
- Etomidate, propofol and sodium pentothal
  - Greater sensitivity
  - Higher brain sensitivity
  - Decreased clearance
- Opioids
  - 50% ↓ in fentanyl requirements between the ages of 20-89 years
  - Alfentanil and sufentanil—50% ↑ in sensitivity
  - Remifentanil—30% ↓ in clearance due to drop in esterase activity
- Muscle relaxants
  - Prolonged onset and duration of action
  - Time from 75% to 25% block is ↑ by 200% !!

**Table 2. Suggested Intravenous Drug Doses**

| | Drugs | Young Patient | Elderly Patient |
|---|---|---|---|
| Sedative/Hypnotics | Midazolam | 0.05 mg/kg | 0.02 mg/kg |
| | Propofol | 2-2.5 mg/ kg | 1-2 mg/kg |
| | **Maintenance:** | **100-200 µg/kg/min** | **50-100 µg/kg/min** |
| | Ketamine | 0.5–2mg/kg | 0.3-1.5mg/kg |
| | Etomidate | 0.2-0.3 mg/kg | 0.1-0.2mg/kg |
| | Thiopental | 3-5 mg/kg | 1.5-3 mg/kg |
| Opiates | Fentanyl | 1-2 µg/kg | 0.5-1 µg/kg |
| | Morphine | 0.03-0.06 mg/kg | 0.02-0.03 mg/kg |
| | Sufentanil | 0.5–10 µg/kg | 0.25-5 µg/kg |
| | Remifentanil | Bolus: 0.1 µg/kg | 0.05 µg/kg |
| | **Maintenance:** | **0.5–2 µg/kg/min** | **0.3-1.5 µg/kg/min** |
| Neuromuscular Blocking Drugs | Succinylcholine | 0.5–1.0 mg/kg | 0.5-1.0 mg/kg |
| | Rocuronium | 0.1-0.6 mg/kg | 0.05-0.4 mg/kg |
| | Vecuronium | 0.02-0.06 mg/kg | 0.01-0.04 mg/kg |
| | Pancuronium | 0.02-0.1 mg/kg | 0.01-0.05 mg/kg |
| | Cisatracurium | 0.05-0.2 mg/kg | 0.05-0.2 mg/kg |
| | Atracurium | 0.2-0.5 mg/kg | 0.2-0.5 mg/kg |
| | Doxacurium | 0.01-0.03 mg/kg | 0.005-0.03 mg/kg |

The drug doses listed are intended to be guides and must be adjusted according to the clinical situation and needs of each patient. In general, most of the drug doses should be decreased 30-50% in elderly patients. There are some exceptions, such as some of the neuromuscular blocking drugs. Except for succinylcholine, the lower dose for each of the neuromuscular blocking drugs is for maintenance during anesthesia while the higher dose is for intubating conditions. The clinician should consider administering maintenance doses of the neuromuscular drugs less frequently. Young patients are assumed to be around 30 yr old, while elderly patients are greater than 70 yr old.

Anesthesiology




Rivera, Richard; Antognini, Joseph F. Anesthesiology. 110(5):1176-1181, May 2009.

# EBP: Evidence *for* POCD

- **Monk, Terri G.; Weldon, B Craig; Garvan, Cyndi W.; Dede, Duane E.; van der Aa, Maria T.; Heilman, Kenneth M.; Gravenstein, Joachim S. Anesthesiology. 108(1):18-30, January 2008.**
- **"Predictors of Cognitive Function after Major Noncardiac Surgery"**
  - Prospective cohort study evaluating the incidence of POCD in three age populations (young, middle age and the elderly)
    - early (hospital discharge) and late (3 months post surgery)
    - Same neuropsychological methodology as the landmark ISPOCD1 study (elderly population)
    - ISPOCD2 study evaluated two age populations (middle-age and elderly)

# Monk et al—Demographic data showing three age groups

**Table 3. Baseline Characteristics of the Patients and Control Subjects**

| | Young, 18–39 yr | | | Middle-aged, 40–59 yr | | | Elderly, ≥ 60 yr | | |
|---|---|---|---|---|---|---|---|---|---|
| | Patients (n = 331) | Controls (n = 74) | *P* Value | Patients (n = 378) | Controls (n = 74) | *P* Value | Patients (n = 355) | Controls (n = 62) | *P* Value |
| Age, yr | 30.5 ± 6.0 | 30.1 ± 6.3 | 0.6263 | 49.9 ± 5.6 | 49.6 ± 6.0 | 0.7222 | 69.9 ± 6.8 | 68.5 ± 5.2 | 0.1996 |
| Sex, % | | | | | | | | | |
| Male | 30 | 42 | 0.0556 | 35 | 27 | 0.2263 | 44 | 42 | 0.7830 |
| Female | 70 | 58 | | 65 | 73 | | 56 | 58 | |
| Years of education | 13.4 ± 2.3 | 13.9 ± 2.8 | 0.3367 | 13.6 ± 2.8 | 13.3 ± 2.7 | 0.2340 | 13.4 ± 2.8 | 13.7 ± 2.7 | 0.4537 |
| BDI score | 7.1 ± 7.0 | 5.0 ± 5.8* | 0.0107 | 7.7 ± 7.3 | 5.12 ± 6.1* | 0.0004 | 5.9 ± 5.1 | 6.2 ± 5.5 | 0.7446 |
| STAI score | | | | | | | | | |
| Trait scale | 34.1 ± 10.0 | 33.8 ± 10.0 | 0.7884 | 32.8 ± 9.9 | 32.1 ± 9.6 | 0.5955 | 30.0 ± 8.3 | 31.9 ± 8.2 | 0.0614 |
| State scale | 38.4 ± 12.2 | 38.0 ± 13.6 | 0.6779 | 37.3 ± 11.7 | 36.0 ± 12.2 | 0.3121 | 33.4 ± 11.3 | 36.7 ± 12.9 | 0.0791 |
| MMSE score | 29.3 ± 1.1 | 29.6 ± 0.8 | 0.0704 | 29.2 ± 1.2 | 29.3 ± 1.2 | 0.2617 | 28.7 ± 1.5 | 29.0 ± 1.4 | 0.0979 |

Plus–minus values are mean ± SD.

* Significant difference between patients and controls.

BDI = Beck Depression Inventory; MMSE = Mini-Mental State Examination; STAI = State Trait Anxiety Inventory.



# Monk et al--Neuropsychological test results of all three groups

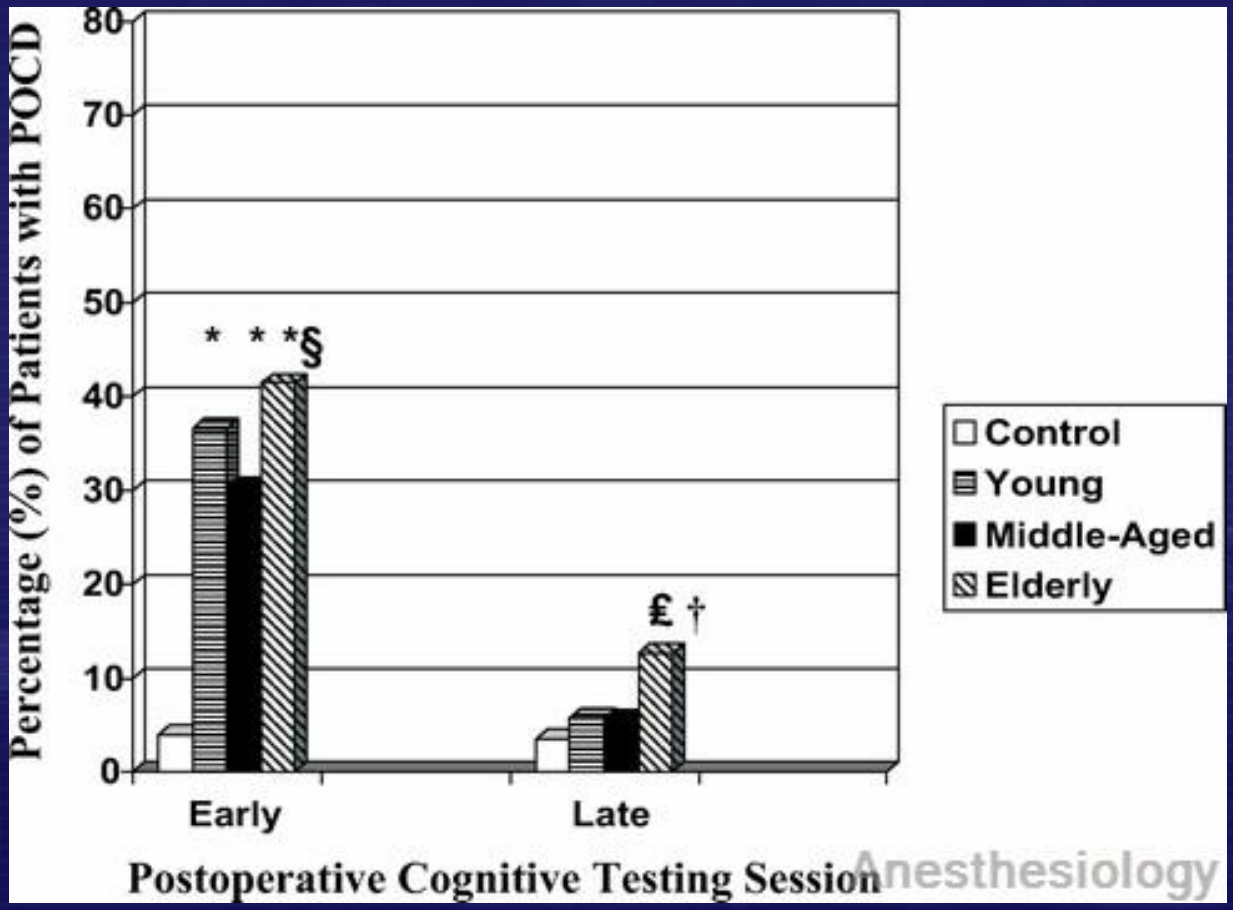
**Table 4. Neuropsychological Test Results for the Patients at Baseline and 3 Months after Surgery**

| | Young Patients Baseline (n = 331) | Young Patients 3 Months after Surgery (n = 282) | Middle-aged Patients Baseline (n = 378) | Middle-aged Patients 3 Months after Surgery (n = 336) | Elderly Patients Baseline (n = 355) | Elderly Patients 3 Months after Surgery (n = 308) |
|---|---|---|---|---|---|---|
| Cumulative learning, number of words | 30.4 ± 5.6 | 31.0 ± 6.2 | 29.2 ± 6.1 | 30.4 ± 6.4 | 25.5 ± 6.0 | 26.4 ± 6.1 |
| Delayed verbal recall, number of words | 10.4 ± 2.9 | 10.7 ± 2.9 | 10.1 ± 2.9 | 10.2 ± 3.2 | 8.3 ± 3.1 | 8.4 ± 3.1 |
| Concept Shifting Test, part C, time in seconds | 26.7 ± 9.3 | 25.1 ± 8.9 | 32.7 ± 15.2 | 30.4 ± 11.5 | 41.8 ± 19.1 | 40.0 ± 17.4 |
| Concept Shifting Test, part C, number of errors | 0.5 ± 1.1 | 0.6 ± 1.4 | 0.6 ± 1.4 | 0.7 ± 1.8 | 0.5 ± 1.1 | 0.8 ± 1.8 |
| Stroop test, part 3, time in seconds | 39.1 ± 10.6 | 35.1 ± 10.2 | 47.4 ± 12.7 | 42.9 ± 12.2 | 56.5 ± 16.1 | 53.4 ± 16.9 |
| Stroop test, part 3, number of errors | 1.0 ± 1.8 | 0.6 ± 1.9 | 1.4 ± 2.5 | 0.8 ± 1.9 | 2.5 ± 4.3 | 1.7 ± 3.2 |
| Letter–Digit Coding, number of correct answers | 39.4 ± 7.7 | 40.7 ± 7.6 | 34.2 ± 6.9 | 35.8 ± 7.1 | 28.9 ± 7.3 | 30.3 ± 7.2 |

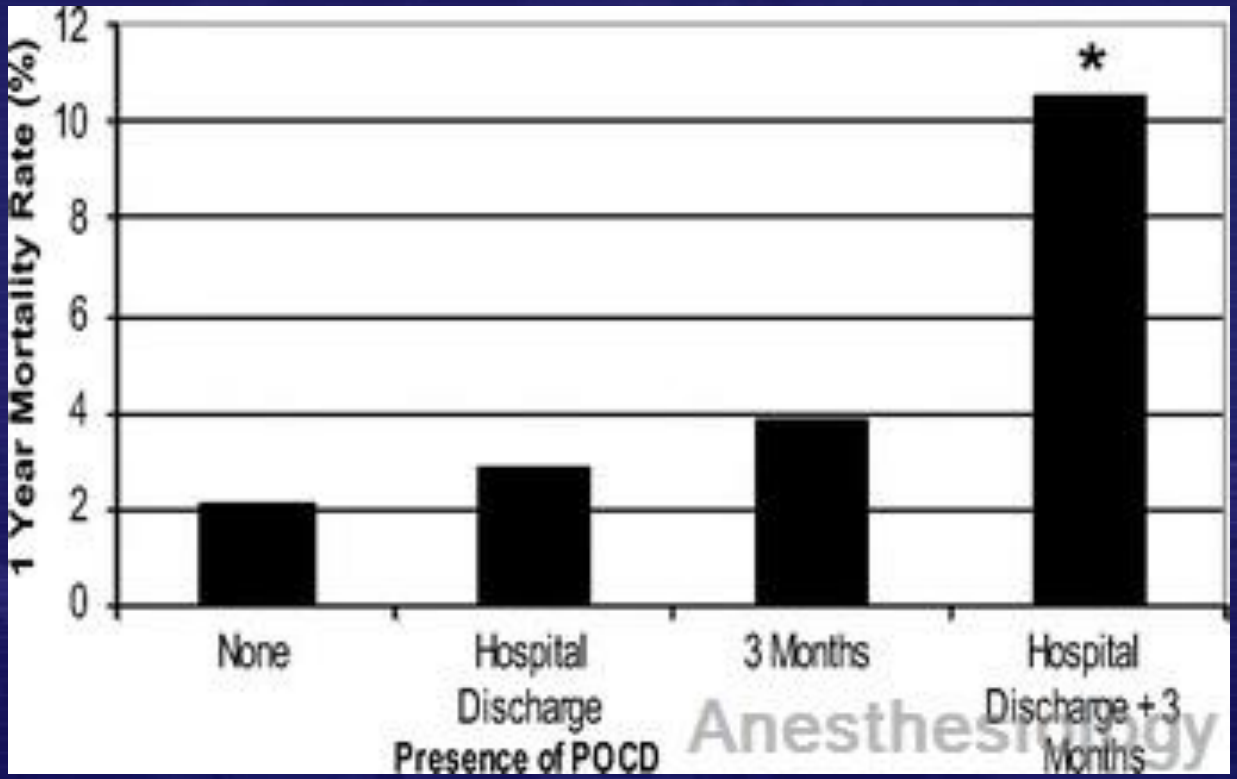
Values are mean ± SD.



# Monk et al—Postoperative cognitive test results



# Monk et al—Presence of POCD and incidence of mortality



# Monk et al—Predictors of POCD

**Predictive factors**

- Increasing age
- Lower level of education
- History of previous CVA with no residual impairment
- POCD at hospital discharge

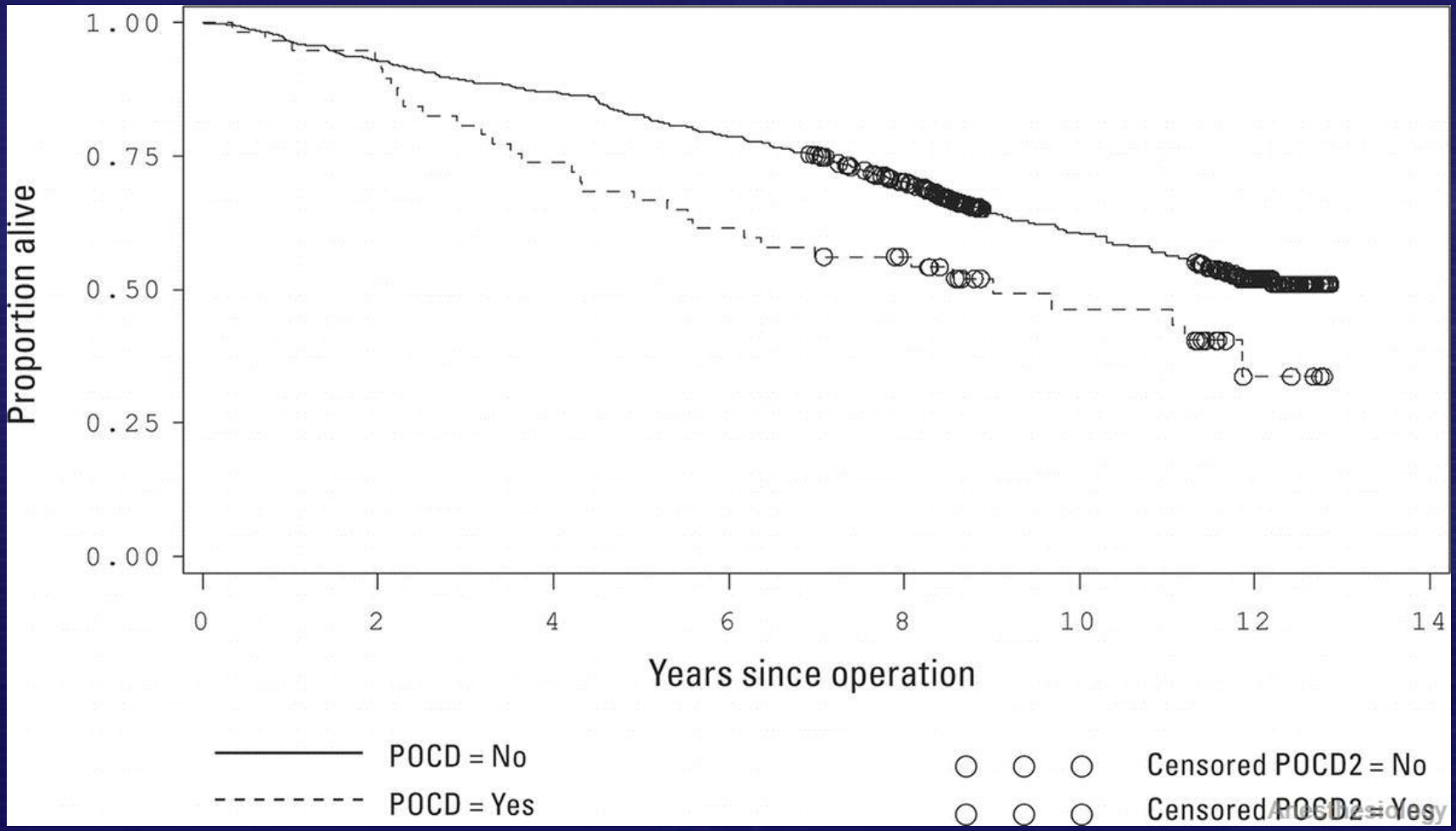
**Studied factors**

- Sex
- History of depression or anxiety
- ASA physical status
- Comorbidities
- Type or duration of surgery
- ICU stay
- Delirium during hospital stay
- Second operation after initial surgery
- Hypertension, MI
- NYHA functional classification
- Use of opioids before testing

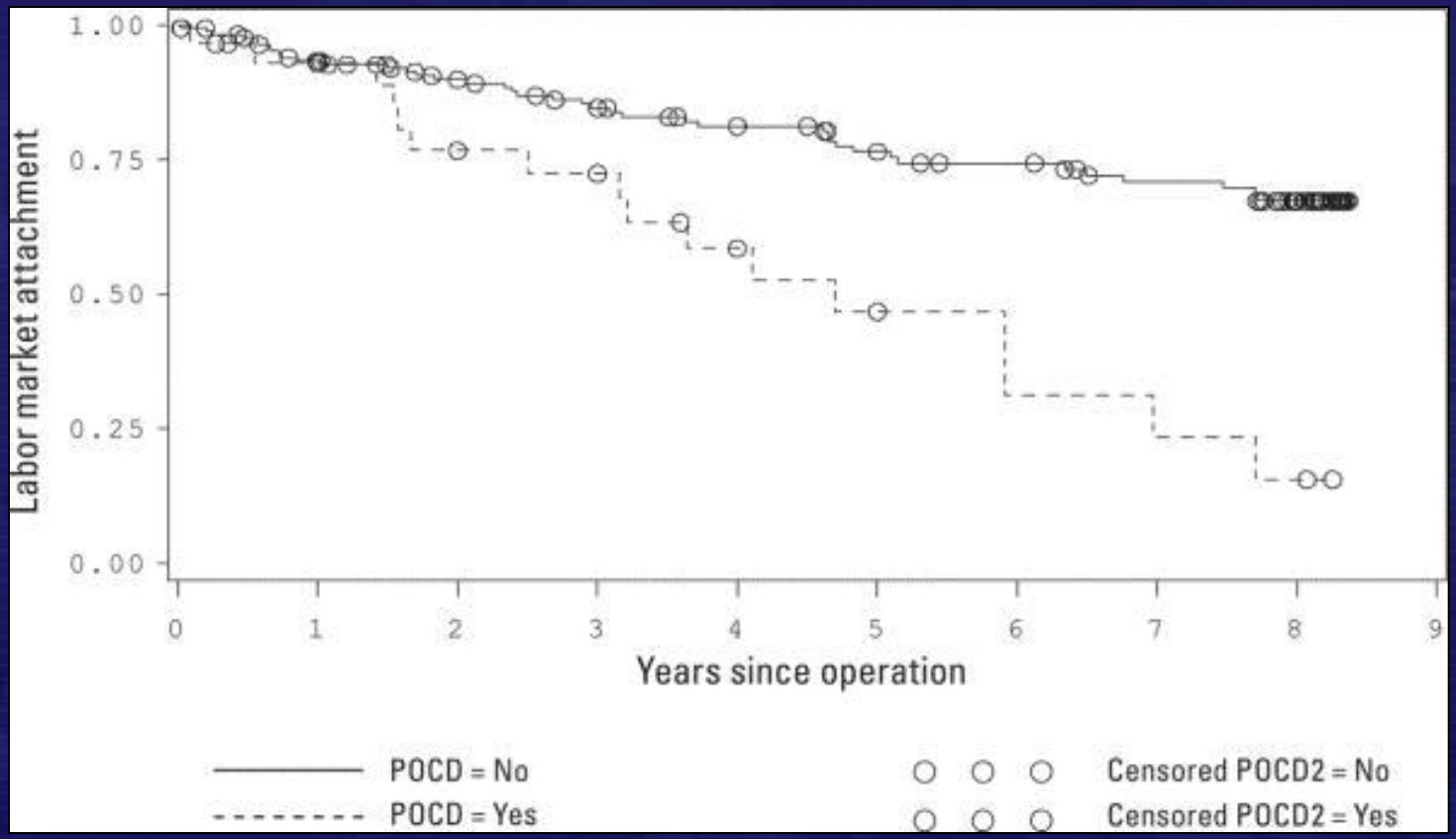
# EBP: Evidence *for* POCD

- **Steinmetz, Jacob; Christensen, Karl Bang; Lund, Thomas; Lohse, Nicolai; Rasmussen, Lars S.; the ISPOCD Group Anesthesiology. 110(3):548-555, March 2009.**
- **"Long-term consequences of Postoperative Cognitive Function"**
  - Observational study of 720 Danish patients enrolled in multicenter studies of POCD between November 1995 and October 2000
    - Cognitive function assessed before, 1 week and 30 days, after non-cardiac surgery
    - Obtained data on survival, and level of function (withdrawal from labor market) for 7 to 14 years post date of surgery
  - Findings
    - ↑ number of patients with POCD at 3 months showed an higher rates of mortality and lower rates of return to function (less return to labor market)

# Steinmetz et al—POCD at 3 months and long-term mortality



# Steinmetz et al—POCD at 3 months and long-term and long-term return to labor force

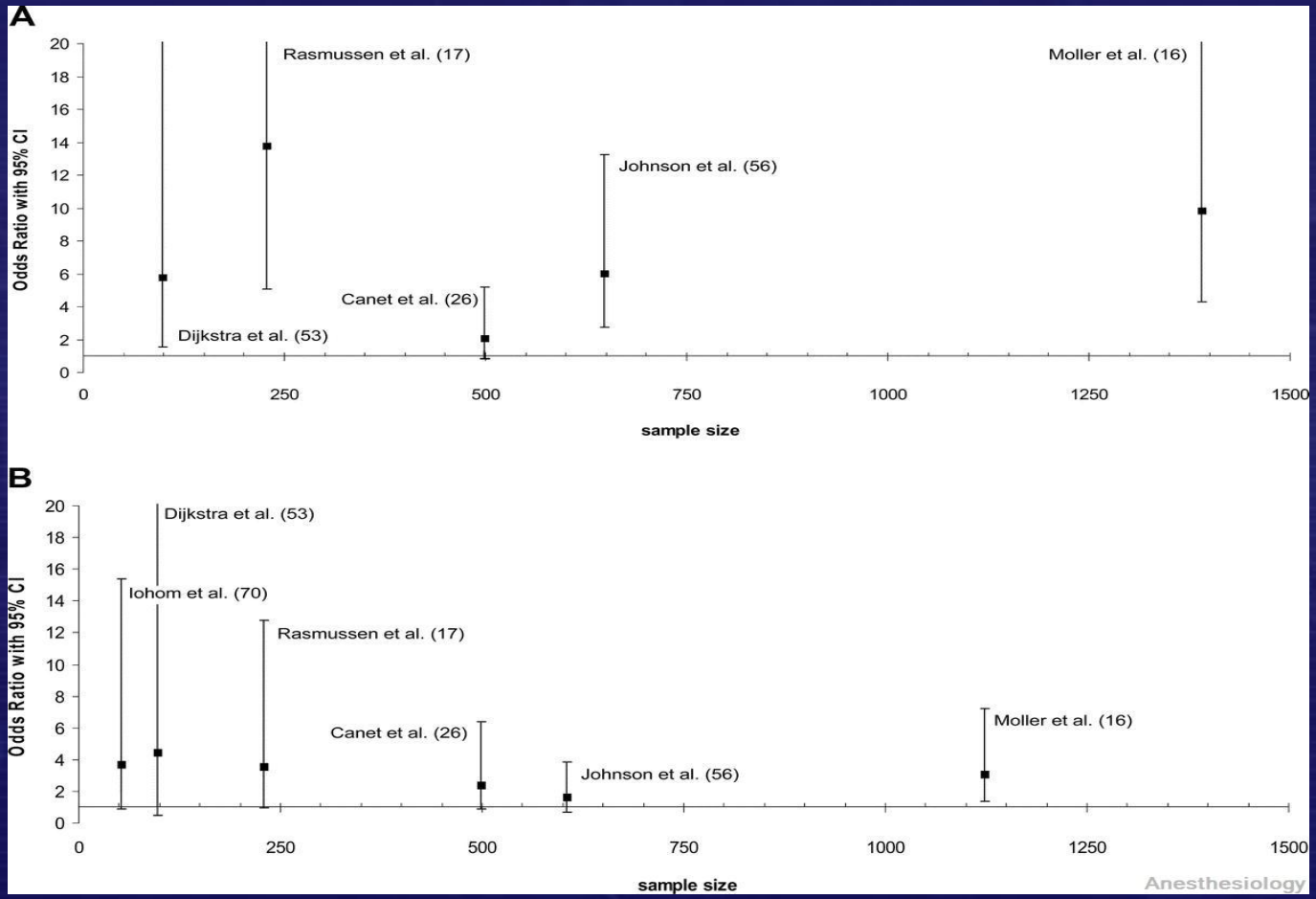


# EBP: *Maybe* evidence for POCD?

- **Newman, Stanton; Stygall, Jan; Hirani, Shashivadan; Shaefi, Shahzad; Maze, Mervyn Anesthesiology. 106(3):572-590, March 2007.**
- **"Postoperative Cognitive Dysfunction after Noncardiac Surgery: A Systematic Review"**

- Systematic review on the research into postoperative cognitive dysfunction
  - Review of citations from Medline, Embase, PsychInfo, and the Cochrane Library
  - Randomized control trials and observational studies
  - Major focus of review:
    - Study design
    - Number of participants
    - Type of surgery and anesthesia
    - Number and timing of assessments

# Newman et al—Systematic review of POCD studies



# EBP: *No* evidence for POCD

- **Avidan MS et al Anesthesiology 111:964-970, Nov 2009**
- **"Long-term Cognitive Decline in Older Subjects was Not Attributable to Noncardiac Surgery or Major Illness**

- Retrospective cohort study of participants tested annually at the Washington University Alzheimer's Disease Research Center
  - Three cohorts: surgical, no surgery/no illness, no surgery/illness
  - Neuropsychological assessment before event and one year after event
  - *Not in keeping with other mainstream studies that test at more frequent intervals (hospital discharge and three months post surgery)*

# EBP from a RCT: YES, POCD does exist!

- **Höcker et al. Anesthesiology 110:1068-1076 May 2009**
- **"Postoperative neurocognitive dysfunction in elderly patients after xenon versus propofol anesthesia for major noncardiac surgery"**

- 101 patients aged 65-83 years old undergoing major abdominal or urologic surgery
- Randomized, double-blinded controlled pilot study
- Patients received sufentanil with either xenon or propofol
- No statistically significant differences noted

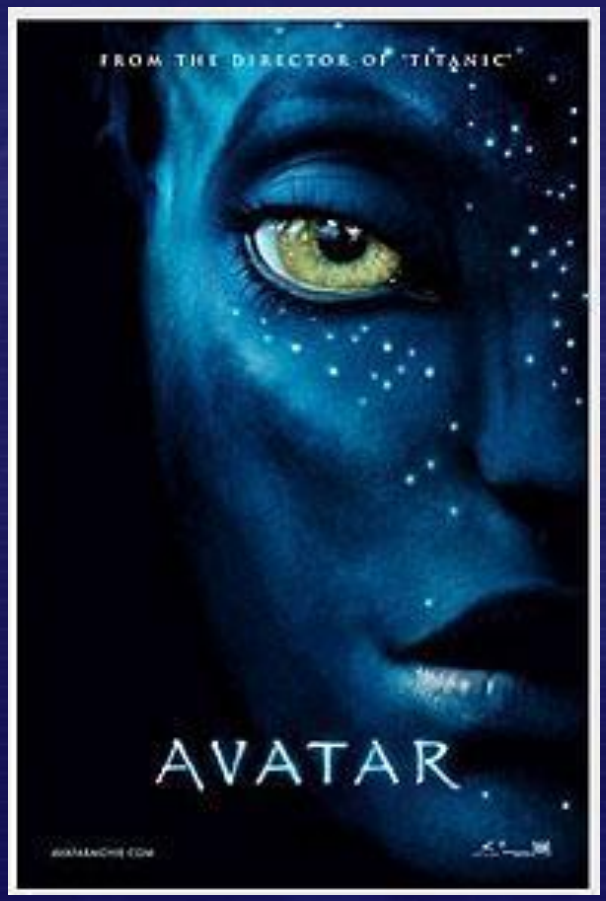
| | Xenon | Propofol |
|---|---|---|
| 1 day postop | 22 (44%) | 25 (50%) |
| 6 days postop | 6 (12%) | 9 (18%) |
| 30 days postop | 3 (6%) | 6 (12%) |

# What can we do about POCD?

- How many of these disturbances fail to resolve over time?
- Can these problems push some elderly patients prematurely into dependency?
- Can we preoperatively identify patients at risk?
- Can we prevent the problem?
- Is the problem even related to anesthesia or is it due to the impact of hospitalization, drugs unrelated to anesthesia, their disease process, or changes brought about as a result of their surgery?

# The Future

- Can we find a new anesthetic agent that is devoid of neurotoxicity?
- Which studies should be designed to establish evidence for the incidence and guidelines for the prevention of POCD?
- Will we routinely do a “mini” cognitive test before and several days after surgery?
- What about antiinflammatory mediators to prevent inflammation?
- Can a brain monitor identify decline?



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