Anesthesia, Surgery & Dementia: A smoking gun – where’s the victim?

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Perelman School of Medicine, University of Pennsylvania
Philadelphia, PA 19104
Disclosures:

Avid Radiopharmaceuticals (Lilly) (research funding)
One out of eight people age 65 or older has Alzheimer's. The number of people with the disease doubles for every 5-year age interval beyond age 65.

Projections are that ~15 million people will have Alzheimer’s by 2050, and more than half of all people will be affected in some way by the disease.
Total *direct* cost of AD care in 2013 = $203 B

In 2050, expected to be $1.2 T
“Currently, firm conclusions cannot be drawn about the association of any modifiable risk factor with cognitive decline or Alzheimer’s disease.”

“Evidence is insufficient to support the use of pharmaceutical agents or dietary supplements to prevent cognitive decline or Alzheimer’s disease.”
There is no *cure* – major current effort is to *delay*…

Approaches:

1. Identify neuropathologic mechanisms and design therapies.
2. Identify environmental contributions and eliminate or modify.

The FASEB Journal • Research Communication

Moderate consumption of Cabernet Sauvignon attenuates Aβ neuropathology in a mouse model of Alzheimer’s disease

Jun Wang,* Lap Ho,* Zhong Zhao,* Ilana Seror,* Nelson Humala,* Dara L. Dickstein,* Meenakshisundaram Thiyagarajan,* Susan S. Percival,§ Sinacher T. Tjalkett§ and Giulio Maria Bolognini**

http://www.cardiothoracicsurgery.org/content/7/1/26

RESEARCH ARTICLE

Auditory stimulation of opera music induced prolongation of murine cardiac allograft survival and maintained generation of regulatory CD4^+CD25^+ cells

Masateru Uchiyama¹,²,³, Xiangyuan Jin²,³, Qi Zhang², Toshihito Hirai⁵, Atsushi Amano¹, Hisashi Bashuda³ and Masanori Niimi²,³
Could surgery be an environmental factor?

Common anecdote:
“My father (grandfather, uncle mother, brother, etc.) hasn’t been himself since the surgery”

Half of all people have surgery in their lifetime
Can anesthetics contribute to Alzheimer Disease?
The amyloid cascade hypothesis:

APP processing → Normal $\alpha$-protein → Intermediates → Amyloid fibrils → DEMENTIA

Neuronal degeneration → Amyloid plaques
Inhaled Anesthetic Enhancement of Amyloid-β Oligomerization and Cytotoxicity

Roderic G. Eckenhoff, M.D.,* Jonas S. Johansson, M.D., Ph.D.,† Huafei Wei, M.D., Ph.D.,‡ Anna Carnini, Ph.D.,§ Baolin Kang, M.D., Wenlin Wei, M.D.,# Ravindernath Pidikiti, M.D.,** Jason M. Keller, B.Sc.,‖ Maryellen F. Eckenhoff, Ph.D.,‖‖ Neurobiology of Disease

The Inhalation Anesthetic Isoflurane Induces a Vicious Cycle of Apoptosis and Amyloid β-Protein Accumulation

Zhongcong Xie, Yuanlin Dong, Uta Maeda, Robert D. Moir, Weiming Xia, Deborah J. Culley, Gregory Crosby, and Rudolph E. Tanzi

Current Alzheimer Research, 2007, 4, 233-241

Inhaled Anesthetic Modulation of Amyloid β₁-₄₀ Assembly and Growth

Anna Carnini, J.D. Lear, and R.G. Eckenhoff

1 Steacie Institute of Molecular Sciences, National Research Council, 100 Sussex Drive, Ottawa, Ontario, ON, Canada KIA 0R6; 2 Department of Biochemistry and Biophysics, The Johnson Research Foundation, University of Pennsylvania School of Medicine

Anesthesia Leads to Tau Hyperphosphorylation through Inhibition of Phosphatase Activity by Hypothermia

Emmanuel Planed, Karl E. G. Richter, Charles E. Nolan, James E. Finley, Li Liu, Yi Wen, Pavan Krishnamurthy, James E. Finley, Li Liu, Yi Wen, Pavan Krishnamurthy, Joel B. Schachter, Robert B. Nelson, Lit-Fui Lau, and Karen E. Duff

Anesthesiology 2008; 108:251–60

The Common Inhaleional Anesthetic Isoflurane Induces Apoptosis via Activation of Inositol 1,4,5-Trisphosphate Receptors

Huafeng Wei, M.D., Ph.D.,* Ge Jiang, M.D.,† Hui Yang, M.D.,‡ Qiujun Wang, M.D.,§ Brian Hawkins, Ph.D., Muniswamy Madesh, Ph.D.,# Shouping Wang, M.D.,** Roderic G. Eckenhoff, M.D.,‖‖
Biological relevance.

Tg2576 (APPsw)

Halothane enhanced plaque load at 14d

12-month old Tg 2576 mice are compromised

No incremental effect of either anesthetic.

Too early? Floor effect? Plaque unrelated to behavior?

Can surgeons share the blame?

A = Controls
B = Anesthesia (IV)
C = Anesthesia + splenectomy
Tumor necrosis factor-α triggers a cytokine cascade yielding postoperative cognitive decline

Niccolò Terrando\textsuperscript{a,b}, Claudia Monaco\textsuperscript{c}, Daqing Ma\textsuperscript{b}, Brian M. J. Foxwell\textsuperscript{c-1}, Marc Feldmann\textsuperscript{c-2}, and Mervyn Maze\textsuperscript{a,b,2}

Surgery

Anesthesia
Anti-inflammatory (NSAID) use and AD

Does Superimposed Inflammation Accelerate Neurodegeneration?

Preclinical:


Anesthesia = 30 min Desflurane 1.5 MAC
Surgery = Laparotomy, cecal excision.

3XTg  WT

3 wks Post-op

13 wks Post-op

Annals Surgery 2013; 257:439-48
Surgery enhances Alzheimer pathogenesis

24 hrs

Iba-1

# microglia / mm2

WT

3XTg

13 wks

pTau

# of stained neurons / mm2

Des

Des/Surg

plaque density

# of plaques/mm2

Des

Des/Surg

Con

Des

Des/Surg

* p < 0.05
Mechanism of 3XTgAD vulnerability?

Dysfunctional Resolution Pathways
Cholinergic resolution
Does anesthetic choice matter?
BV-2 Microglia cell line, different anesthetics, ± LPS
Propofol mitigates the effect of surgery on long term cognition.
Genomic responses in mouse models poorly mimic human inflammatory diseases

Junhee Seok¹,¹, H. Shaw Warren¹,¹, Alex G. Cuenca²,¹, Michael N. Mindrinos³, Henry V. Baker⁵, Weihong Xu⁶, Daniel R. Richards⁷, Grace P. McDonald-Smith⁸, Hong Gao⁹, Laura Hennessy¹⁰, Celeste C. Finnerty¹¹, Cecilia M. López¹², Shari Honari¹³, Ernest E. Moore¹⁴, Joseph P. Minei¹⁵, Joseph Cuschieri¹⁶, Paul E. Bankey¹⁷, Jeffrey L. Johnson¹⁸, Jason Sperry¹⁹, Avery B. Nathens²⁰, Timothy R. Billiar¹, Michael A. West²¹, Marc G. Jeschke²², Matthew B. Klein²³, Richard L. Gamelli²⁴, Nicole S. Gibran²⁵, Bernard H. Brownstein²⁶, Carol Miller-Graziano²⁷, Steve E. Calvano²⁸, Philip H. Mason²⁹, J. Perren Cobb³⁰, Laurence G. Rahme³¹, Stephen F. Lowry³², Ronald V. Maier³³, Lyle L. Moldawer³⁴, David N. Herndon³⁵, Ronald W. Davis³⁶,³⁷, Wenzhong Xiao³⁸,³⁹, Ronald G. Tompkins⁴,³ and the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program⁴

PNAS  |  February 26, 2013  |  vol. 110  |  no. 9  |  3507–3512
So much for smoke, is there a VICTIM?

Palotas A et al, Eur J Neurology 2007; 14:318
Ehlenbach et al. JAMA 2010; 303:763-770.
Wilson et al, Neurology 2012; 78:950
Chen et al, Br. J. Psychiatry 2014; 204: 188
Sprung et al, Mayo Clinic Proc. 2013; 88: 1
Does surgery or major illness change cognitive decline after age 78? Use of ADRC data.

Association Between Acute Care and Critical Illness Hospitalization and Cognitive Function in Older Adults

William J. Ehlenbach, MD, MSc
Catherine L. Hough, MD, MSc
Paul K. Crane, MD, MPH
Sebastien J. P. A. Haneuse, PhD
Shannon S. Carson, MD
J. Randall Curtis, MD, MPH
Eric B. Larson, MD, MPH

Table 4. Risk of Incident Dementia by Hospitalization Status

<table>
<thead>
<tr>
<th></th>
<th>No Hospitalizations During Study (n = 1601)</th>
<th>One or More Noncritical Illness Hospitalizations (n = 1287)</th>
<th>One or More Critical Illness Hospitalizations (n = 41)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases of incident dementia, No.</td>
<td>146</td>
<td>228</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Risk of incident dementia, HR (95% CI)</td>
<td>1 [Reference]</td>
<td>1.5 (1.3 to 1.9)</td>
<td>1.7 (0.7 to 4.0)</td>
<td>.27</td>
</tr>
<tr>
<td>Adjusted risk of incident dementia, HR (95% CI)</td>
<td>1 [Reference]</td>
<td>1.4 (1.1 to 1.7)</td>
<td>2.3 (0.9 to 5.7)</td>
<td>.09</td>
</tr>
</tbody>
</table>
Cognitive decline after hospitalization in a community population of older persons

Wilson et al, Neurology 2012; 78:950

1871 subjects >65, 71% hospitalized
Anesthesia and Incident Dementia: A Population-Based, Nested, Case-Control Study

Juraj Sprung, MD, PhD; Christopher J. Jankowski, MD; Rosebud O. Roberts, MD; Toby N. Weingarten, MD; Andrea L. Aguilar, SRNA; Kayla J. Runkle, SRNA; Amanda K. Tucker, SRNA; Kathryn C. McLaren, RN; Darrell R. Schroeder, MS; Andrew C. Hanson, BS; David S. Knopman, MD; Carmelina Gurrieri, MD; and David O. Wamer, MD

<p>| TABLE 3. Association Between Exposure to Anesthesia and Subsequent Dementia* |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th><strong>Exposure</strong></th>
<th><strong>Controls</strong></th>
<th><strong>Cases</strong></th>
<th><strong>Odds ratio</strong></th>
<th><strong>95% CI</strong></th>
<th><strong>P value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia (including Alzheimer dementia) (N=877)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Any anesthetic</td>
<td>636 (72.5)</td>
<td>615 (70.1)</td>
<td>0.89</td>
<td>0.73-1.10</td>
<td>.27</td>
</tr>
<tr>
<td>Anesthetic exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>241 (27.5)</td>
<td>262 (29.9)</td>
<td>1.00</td>
<td>Reference</td>
<td>.51</td>
</tr>
<tr>
<td>1</td>
<td>224 (25.5)</td>
<td>211 (24.1)</td>
<td>0.87</td>
<td>0.68-1.12</td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>282 (32.2)</td>
<td>263 (30.0)</td>
<td>0.86</td>
<td>0.67-1.10</td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>130 (14.8)</td>
<td>141 (16.1)</td>
<td>1.00</td>
<td>0.74-1.35</td>
<td></td>
</tr>
<tr>
<td>Cumulative duration of anesthesia (min)b</td>
<td>140 (0-305)</td>
<td>135 (0-307.5)</td>
<td>1.00</td>
<td>0.99-1.01</td>
<td>.86</td>
</tr>
<tr>
<td>Cumulative duration of anesthesia (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>241 (27.5)</td>
<td>262 (29.9)</td>
<td>1.00</td>
<td>Reference</td>
<td>.58</td>
</tr>
<tr>
<td>1-120</td>
<td>163 (18.6)</td>
<td>159 (18.1)</td>
<td>0.90</td>
<td>0.69-1.19</td>
<td></td>
</tr>
<tr>
<td>121-240</td>
<td>195 (22.2)</td>
<td>175 (20.0)</td>
<td>0.83</td>
<td>0.64-1.08</td>
<td></td>
</tr>
<tr>
<td>≥241</td>
<td>278 (31.7)</td>
<td>281 (32.0)</td>
<td>0.93</td>
<td>0.73-1.19</td>
<td></td>
</tr>
<tr>
<td>Duration of longest single exposure (min)</td>
<td>105 (0-165)</td>
<td>100 (0-170)</td>
<td>0.99</td>
<td>0.96-1.02</td>
<td>.49</td>
</tr>
<tr>
<td>Duration of longest single exposure (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>241 (27.5)</td>
<td>262 (29.9)</td>
<td>1.00</td>
<td>Reference</td>
<td>.54</td>
</tr>
<tr>
<td>1-120</td>
<td>268 (30.6)</td>
<td>249 (28.4)</td>
<td>0.86</td>
<td>0.67-1.10</td>
<td></td>
</tr>
<tr>
<td>121-240</td>
<td>280 (31.9)</td>
<td>269 (30.7)</td>
<td>0.89</td>
<td>0.70-1.14</td>
<td></td>
</tr>
<tr>
<td>≥241</td>
<td>88 (10.0)</td>
<td>97 (11.1)</td>
<td>1.02</td>
<td>0.72-1.44</td>
<td></td>
</tr>
</tbody>
</table>
Exposure to general anaesthesia could increase the risk of dementia in elderly

F. Sztark¹, M. Le Goff², D. André¹, K. Ritchie², C. Berr², C. Tzourio², J.F. Dartigues², C. Helmer²

¹Service d'Anesthésie Réanimation, CHU de Bordeaux, ²ISPED-INSERM CR897, Université de Bordeaux
33076 Bordeaux Cedex France

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Model</th>
<th>n=6534, 562 dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>IC 95%</td>
</tr>
<tr>
<td>Anesthesia: yes vs no</td>
<td>1.24</td>
<td>1.04-1.48</td>
</tr>
<tr>
<td>Anesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>general anaesthesia</td>
<td>1.35</td>
<td>1.11-1.63</td>
</tr>
<tr>
<td>local/locoregional anaesthesia</td>
<td>1.12</td>
<td>0.89-1.41</td>
</tr>
</tbody>
</table>
# Risk of dementia after anaesthesia and surgery

Pin-Liang Chen,* Chih-Wen Yang,* Yi-Kuan Tseng, Wei-Zen Sun, Jane-Ling Wang, Shuu-Jiun Wang, Yen-Jen Oyang and Jong-Ling Fuh

**The British Journal of Psychiatry (2014)**

204, 188–193. doi: 10.1192/bjp.bp.112.119610

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## Table 4  Hazard ratios of dementia in the anaesthesia v. control groups, stratified by age and gender

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients with dementia diagnosis in the anaesthesia group n (%)</th>
<th>Patients with dementia diagnosis in the control group n (%)</th>
<th>HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>661 (2.65)</td>
<td>1539 (1.39)</td>
<td>1.99 (1.81–2.17)</td>
<td>1.75 (1.59–1.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>296 (2.40)</td>
<td>583 (1.09)</td>
<td>2.30 (2.00–2.65)</td>
<td>2.01 (1.78–2.37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>365 (2.90)</td>
<td>956 (1.66)</td>
<td>1.80 (1.60–2.03)</td>
<td>1.58 (1.40–1.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–65</td>
<td>91 (0.64)</td>
<td>239 (0.34)</td>
<td>1.90 (1.49–2.42)</td>
<td>1.65 (1.30–2.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;65</td>
<td>570 (5.35)</td>
<td>1300 (3.25)</td>
<td>1.79 (1.62–1.97)</td>
<td>1.70 (1.53–1.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Charlson index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3</td>
<td>91 (0.57)</td>
<td>293 (0.34)</td>
<td>1.90 (1.68–2.16)</td>
<td>1.85 (1.63–2.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥3</td>
<td>570 (6.46)</td>
<td>1246 (5.17)</td>
<td>1.67 (1.45–1.91)</td>
<td>1.63 (1.43–1.87)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HR, hazard ratio.

a. All models are analysed by Cox regressions adjusted for hypertension, hyperlipidaemia, depression and Charlson index.
Inhaled Sevoflurane May Promote Progression of Amnestic Mild Cognitive Impairment: A Prospective, Randomized Parallel-Group Study

Yongzhe Liu, MD, PhD, Ningling Pan, MD, Yaqun Ma, MD, Shengshuo Zhang, MD, PhD, Wenzhi Guo, MD, PhD, Haihong Li, MD, Jingli Zhou, MD, Gang Liu, MD and Minglong Gao, MD, PhD

~200 aMCI patients for spinal surgery, randomized to 1 of 3 groups.

Cognition before and at 2 years post-op. CSF prior to surgery.

<table>
<thead>
<tr>
<th>TABLE 2. Progression of amnestic mild cognitive impairment (MCI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Sevoflurane</td>
</tr>
<tr>
<td>Propofol</td>
</tr>
<tr>
<td>Epidural anesthesia</td>
</tr>
<tr>
<td>Control</td>
</tr>
</tbody>
</table>

\(^a\) P < 0.01 vs. control.
Alzheimer’s disease is a lifelong process. Detection of remote influences is difficult!

WHY BIOMARKERS?

Establish a diagnosis of AD in symptomatic patients

Establish risk of AD in pre-symptomatic patients.

Select patients for interventional trials.

Provide an objective measure of intervention.

Stratify risk in perioperative patients.
## CSF Biomarkers

**ADNI 1 data.**

### Table

<table>
<thead>
<tr>
<th></th>
<th>Tau</th>
<th>$A\beta_{1-42}$</th>
<th>P-Tau$_{181P}$</th>
<th>Tau/$A\beta_{1-42}$</th>
<th>P-Tau$<em>{181P}/A\beta</em>{1-42}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AD (n=102)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>122±58</td>
<td>143±41</td>
<td>42±20</td>
<td>0.9±0.5</td>
<td>0.3±0.2</td>
</tr>
<tr>
<td><strong>MCI (n=200)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>103±61</td>
<td>164±55</td>
<td>35±18</td>
<td>0.8±0.6</td>
<td>0.3±0.2</td>
</tr>
<tr>
<td><strong>NC (n=114)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>70±30</td>
<td>206±55</td>
<td>25±15</td>
<td>0.4±0.3</td>
<td>0.1±0.1</td>
</tr>
</tbody>
</table>

p<0.0001, for each of the 5 biomarker tests for AD vs NC and for MCI vs NC.
For AD vs MCI: p<0.005, Tau; p<0.01, $A\beta_{1-42}$; p<0.01, P-Tau$_{181P}$; p<0.0005, Tau/$A\beta_{1-42}$; p<0.005, P-Tau$_{181P}/A\beta_{1-42}$. Mann-Whitney test.

(Shaw, Trojanowski, etc)
Human CSF Biomarkers:

14 patients, CABG, ave. age = 64,

Eleven patients, nasal endoscopy, lumbar drains. Ave. age = 55
IMAGING BIOMARKERS

- Amyloid-PET
- FDG-PET
- MRI volumes

Normal
AD
Six months after surgery, specific brain regions atrophied more than matched patients who did not have surgery.  (Anesthesiology, 2012)
Working model of neurodegeneration

Anesthesia/surgery

Cognition

Neuropathology

0

Age

100
Working model of neurodegeneration

- Cognition
- Neuropathology

Anesthesia/surgery
Working model of neurodegeneration

- Cognition
- Neuropathology

Anesthesia/surgery
Should we change practice?

If so, HOW?
What should we tell our patients?

ASK QUESTIONS ABOUT ANESTHESIA
Could anesthesia bring on Alzheimer’s?
Summary:
1. Anesthesia/surgery independently contribute to cognitive decline.
2. Lower risk anesthetics?
3. Vulnerable window and subgroups uncertain.
4. Vulnerability may lie in dysfunctional resolution

Where next?
1. Human studies – biomarkers and imaging.
2. Epidemiology of AD and surgery/anesthesia.
3. Informed consent issues.