

Neurocognitive dysfunction post cardiac surgery: How common is it and why does it happen?

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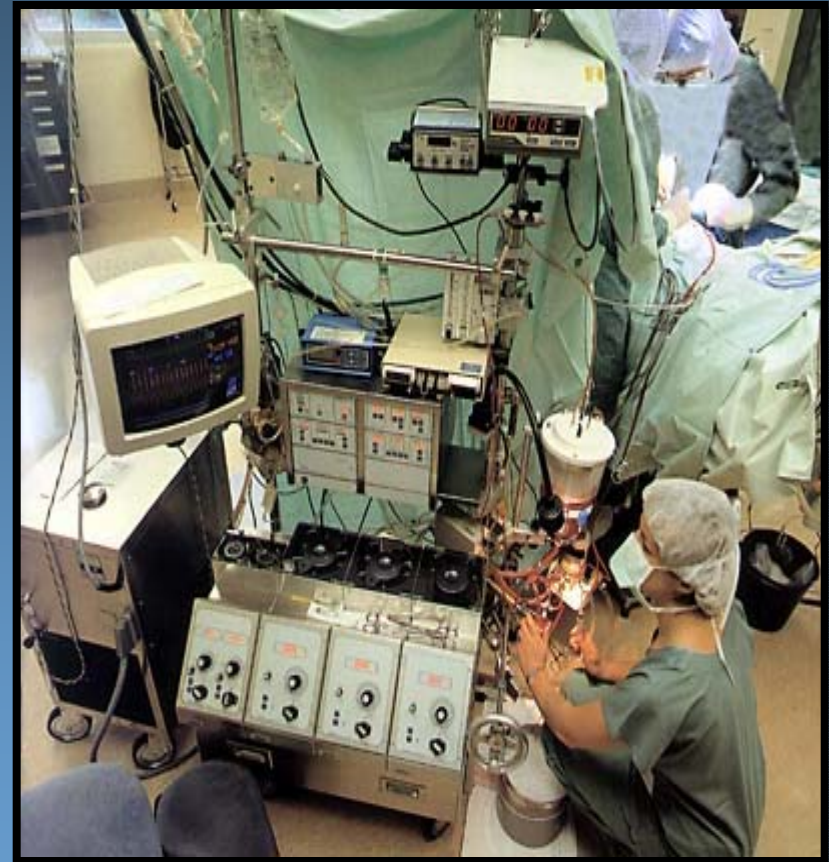
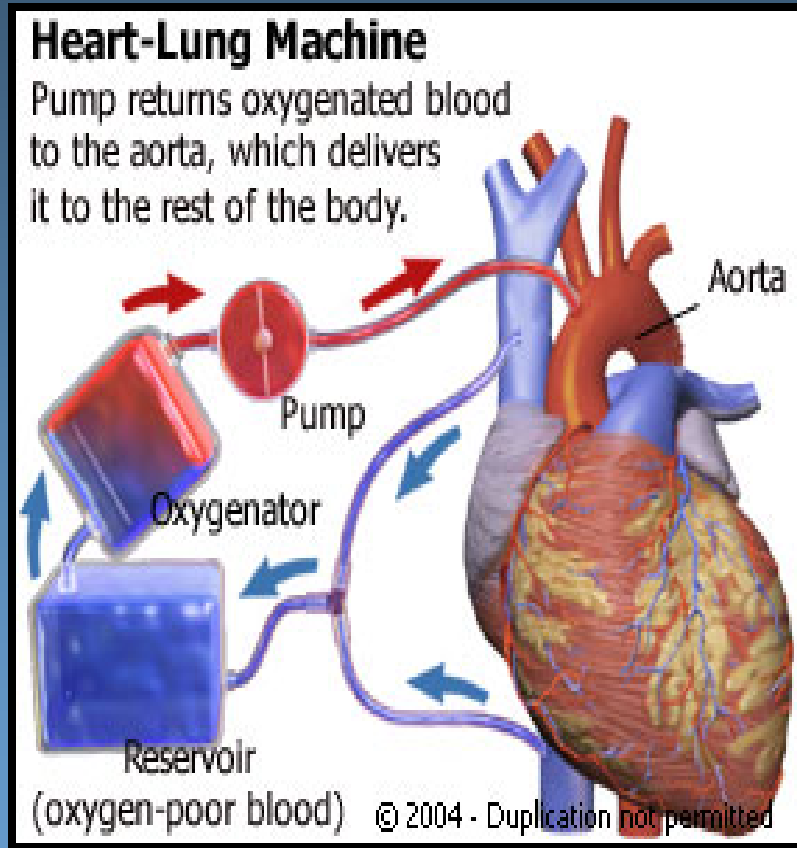


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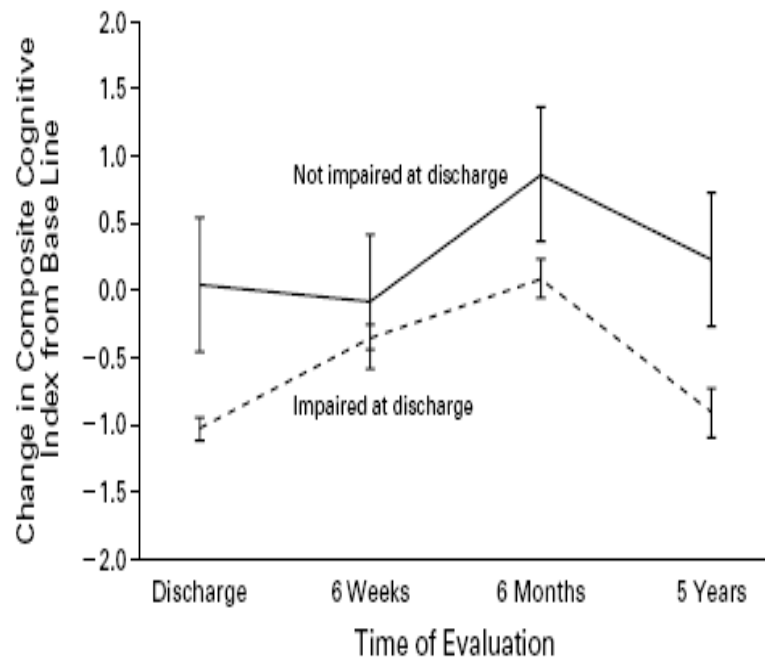
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Modern Heart Lung Machine



LONGITUDINAL ASSESSMENT OF NEUROCOGNITIVE FUNCTION AFTER CORONARY-ARTERY BYPASS SURGERY

MARK F. NEWMAN, M.D., JERRY L. KIRCHNER, B.S., BARBARA PHILLIPS-BUTE, PH.D., VINCENT GAVER, B.S., HILARY GROCCOTT, M.D., ROBERT H. JONES, M.D., DANIEL B. MARK, M.D., JOSEPH G. REVES, M.D., AND JAMES A. BLUMENTHAL, PH.D., FOR THE NEUROLOGICAL OUTCOME RESEARCH GROUP AND THE CARDIOTHORACIC ANESTHESIOLOGY RESEARCH ENDEAVORS INVESTIGATORS*



- Incidence of cognitive decline was:
 - Discharge – 53%
 - Six Weeks - 36%
 - Six Months - 24%
 - Five Years - 42%
- Pattern of early improvement followed by a later decline.

- Cognitive function at discharge was a significant independent predictor of long-term decline ($P < 0.001$).



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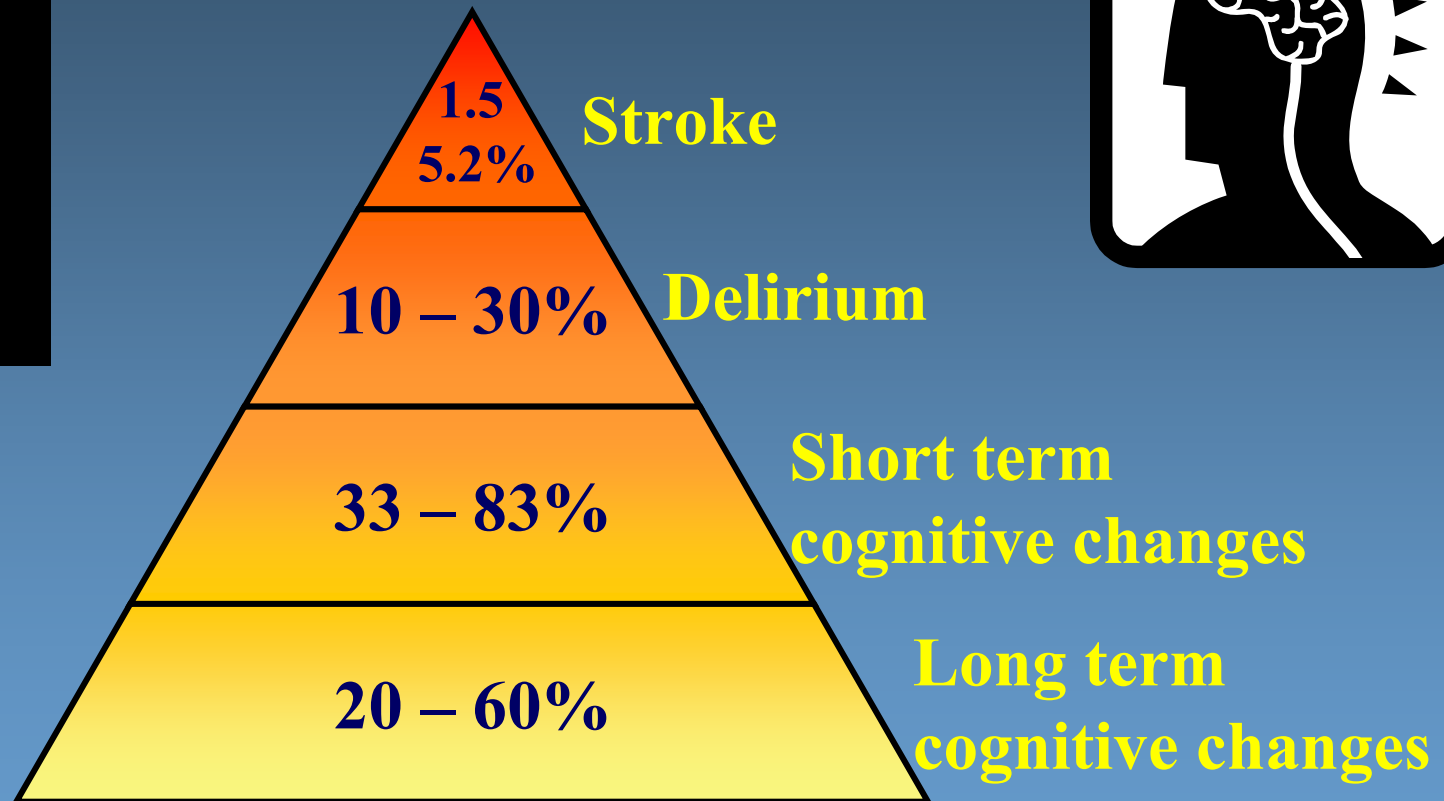
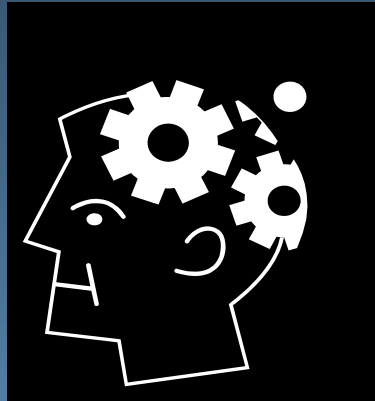
N Engl J Med. 2001 Feb 8;344(6):395-402.

Neurologic dysfunction: Van Dijk et al. Octopus study. JAMA 2007

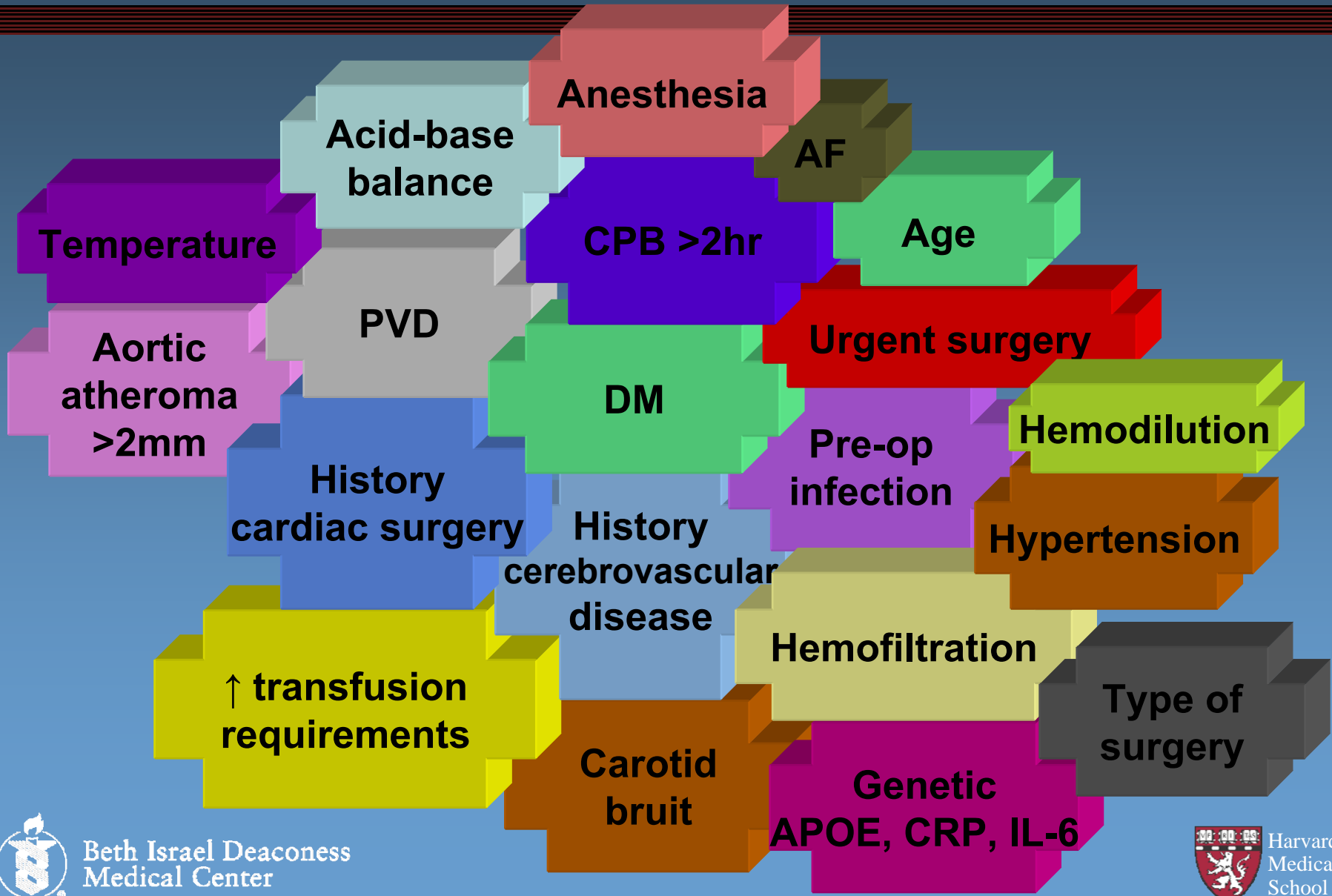
- 281 low-risk CABG patients. Five years after their surgery, surviving patients were assessed
- When using a standard definition of cognitive decline 50.4% of OPCAB pts and 50.4% of std CABG pts had cognitive decline
- When a more conservative definition of cognitive decline was used, 33.3% of OPCAB pts and 35.0% of std CABG pts had cognitive decline
- No differences were observed in anginal status or quality of life.
- The authors conclude that in low-risk patients undergoing CABG surgery, **avoiding the use of cardiopulmonary bypass had no effect on 5-year cognitive or cardiac outcomes.**



Incidence of Adverse Cerebral Outcomes: Is there a difference with off pump vs on pump?



Possible Risk Factors – *Multi-factorial*



CABG (?Bypass)-Induced Brain Edema



Pre-Op



Post-Op



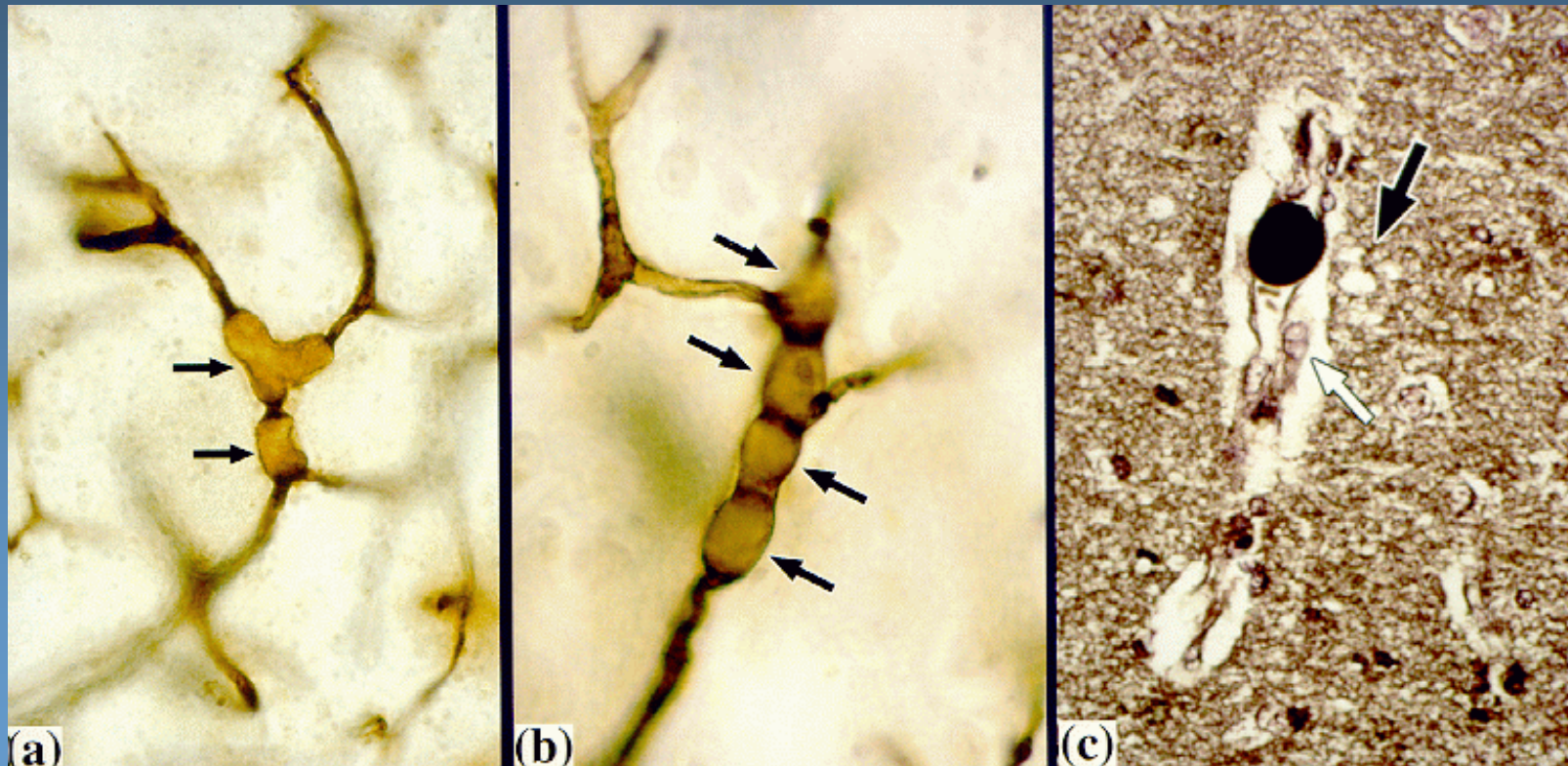
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Harris DNF et al. *Lancet* 1993;342:586

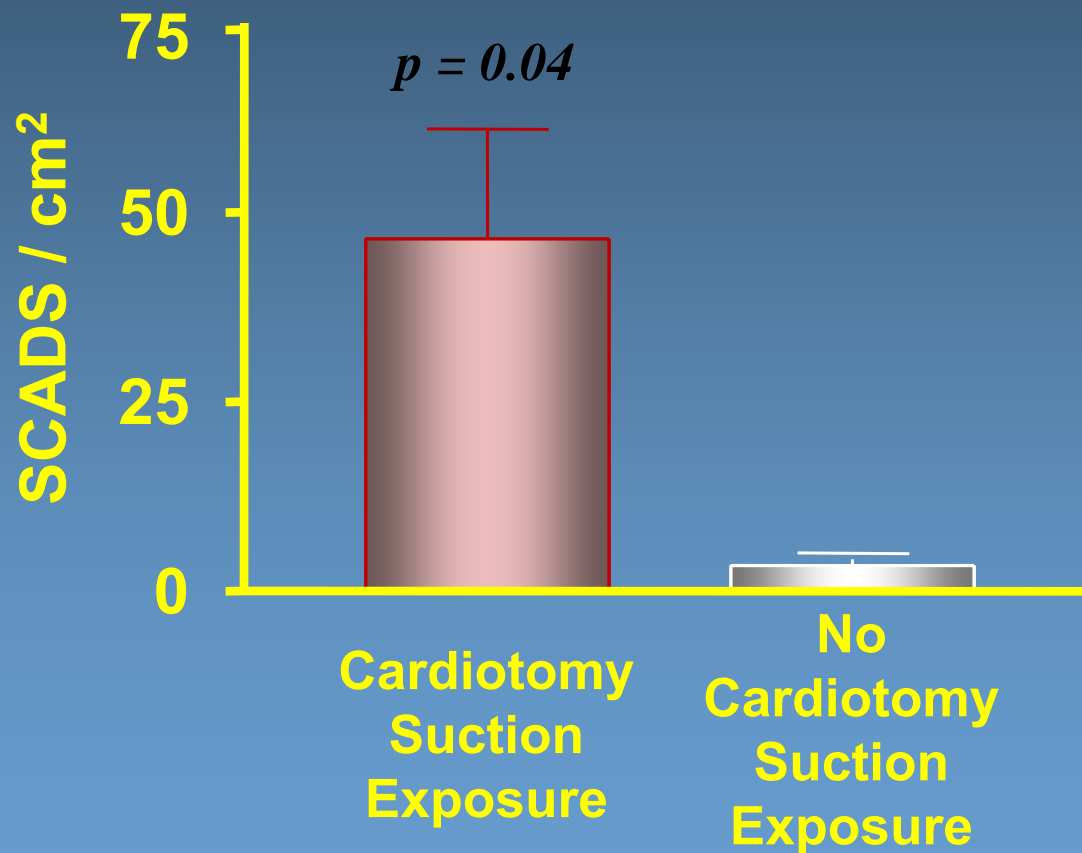


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Small Capillary Arterial Dilatations (SCADs) in Brain Tissue at Autopsy after CPB CABG



SCADs Related to Exposure of Cardiotomy Suction Blood



Canine
Model



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Brooker R et al. Ann Thorac Surg
1998;65:1651



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Reduced Manipulation of the Ascending Aorta During Coronary Surgery Improves Neurobehavioral Outcome.

NINDS, JW Hammon, P.I., DA Stump, Co-P.I., Dates: 1999-2004.

J Thorac Cardiovasc Surg. 2006 Jan;131(1):114-21.

Neurobehavioral Outcomes in High Risk CABG Patients@

	Multi-Clamp	Single-Clamp	OPCab
One Week	60% (25/42)	60% (44/74)	67% (33/47)
One Month	51% (25/49)	32% (27/85)	39% (20/51)
Six Months*	57% (24/42)	29% (22/74)	32% (13/42)*

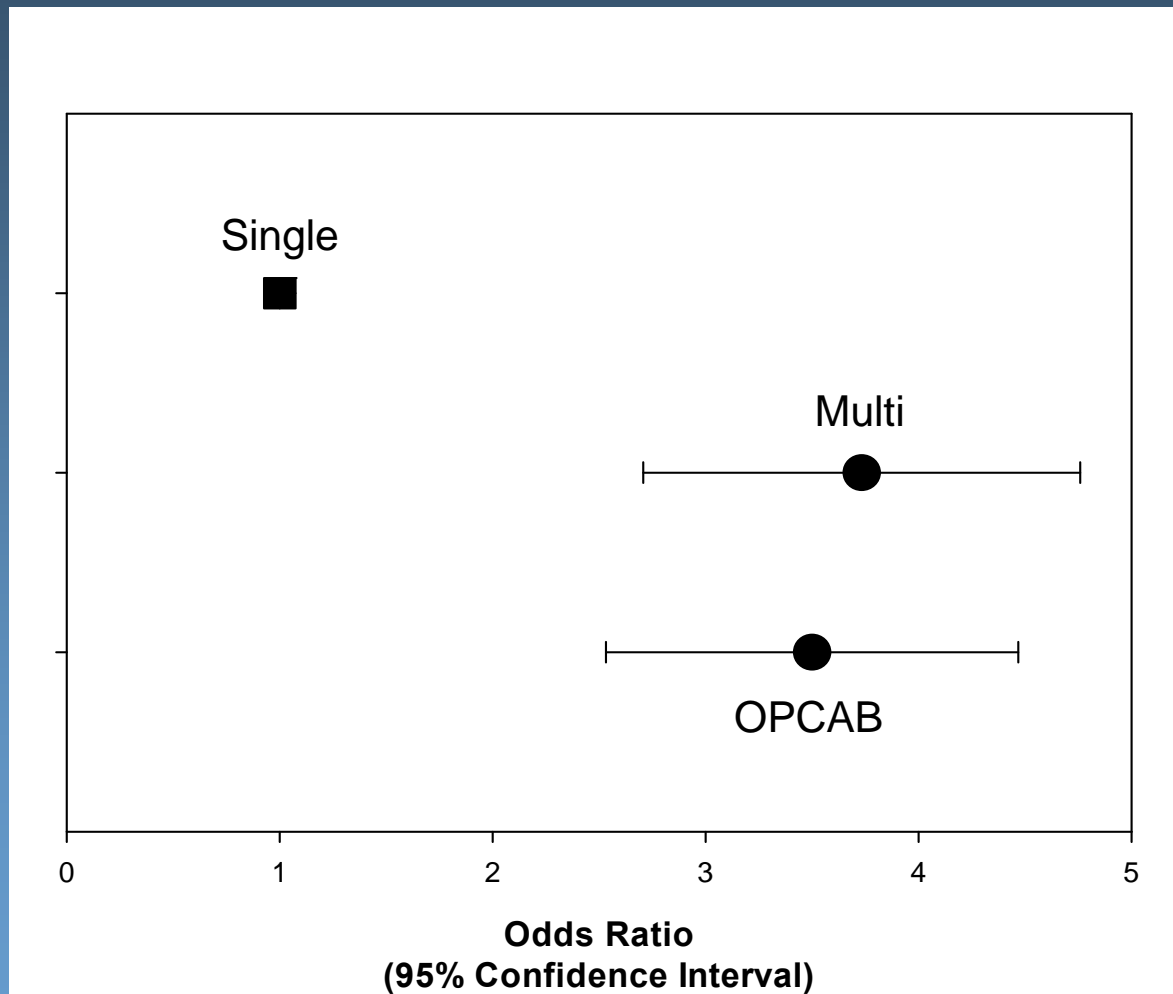


@No aprotinin
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Six month comparisons; $p = 0.007$, All Groups; $p = 0.035$,
OPCAB vs. Multiple
 $p = 0.005$, Multiple vs. Single Chi Square



Odds Ratio of a Persistent Deficit at 6 Months

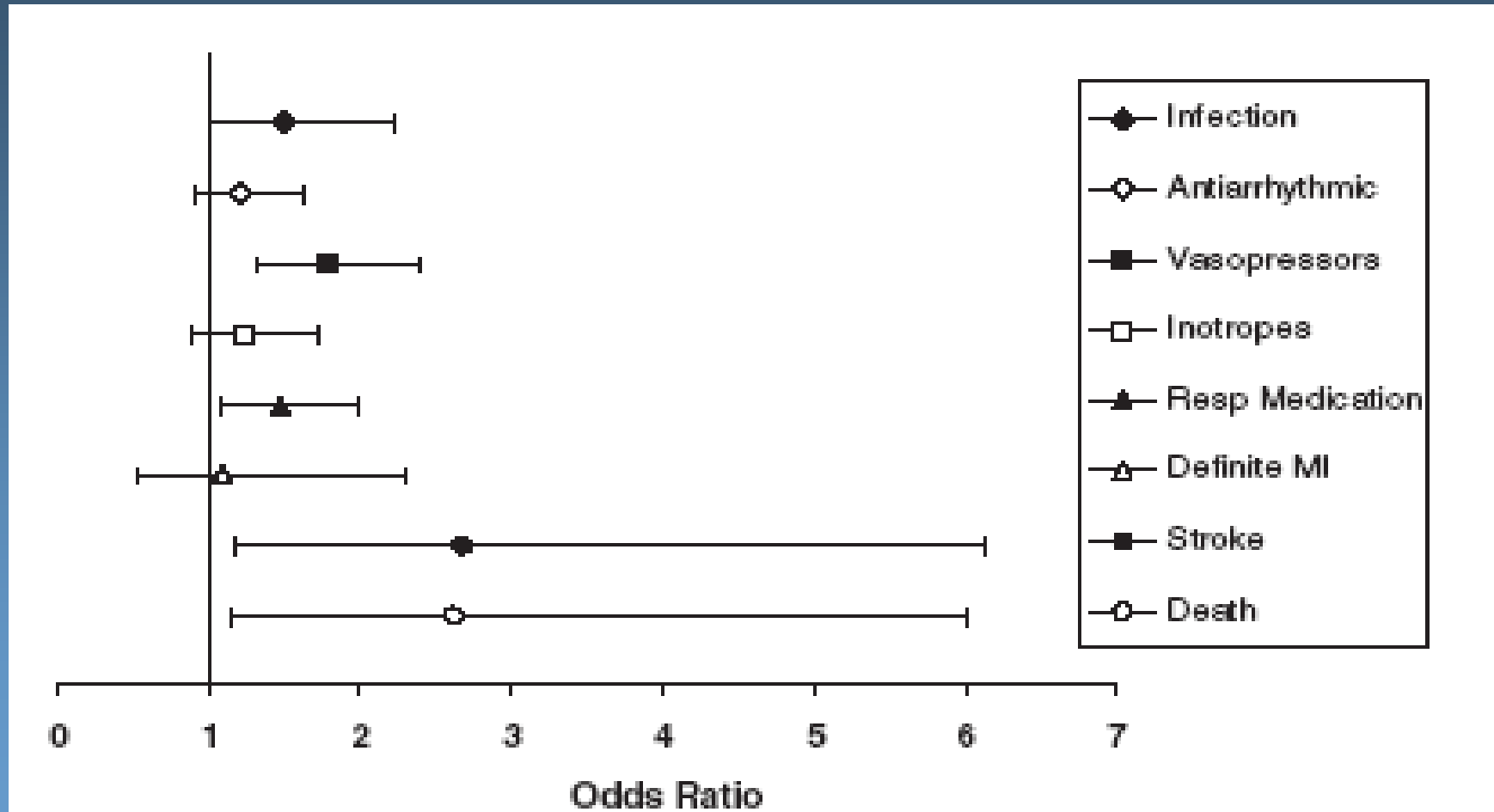


Multi Risk = 3.7 > Single

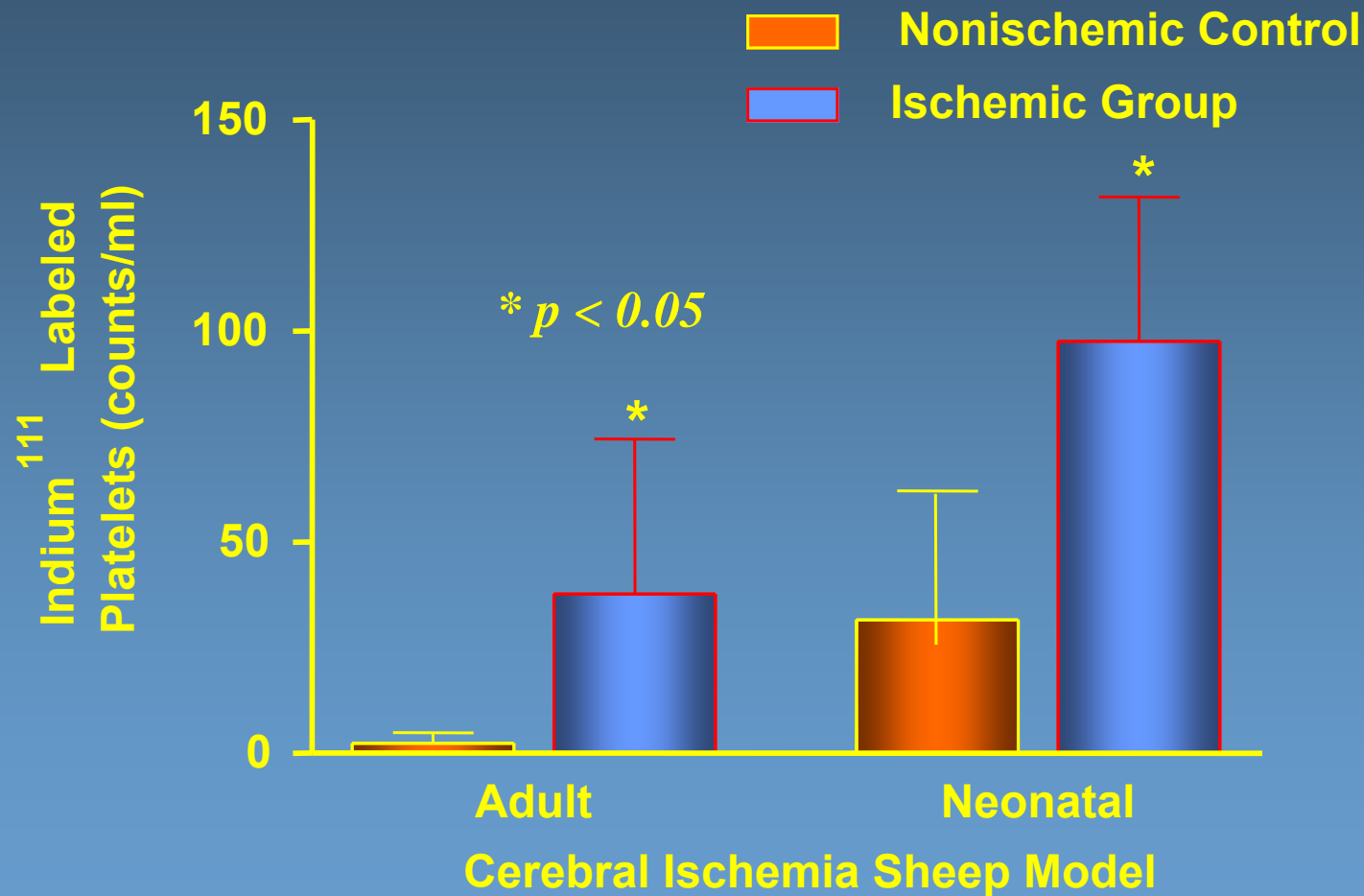
OPCAB Risk = 3.5 > Single



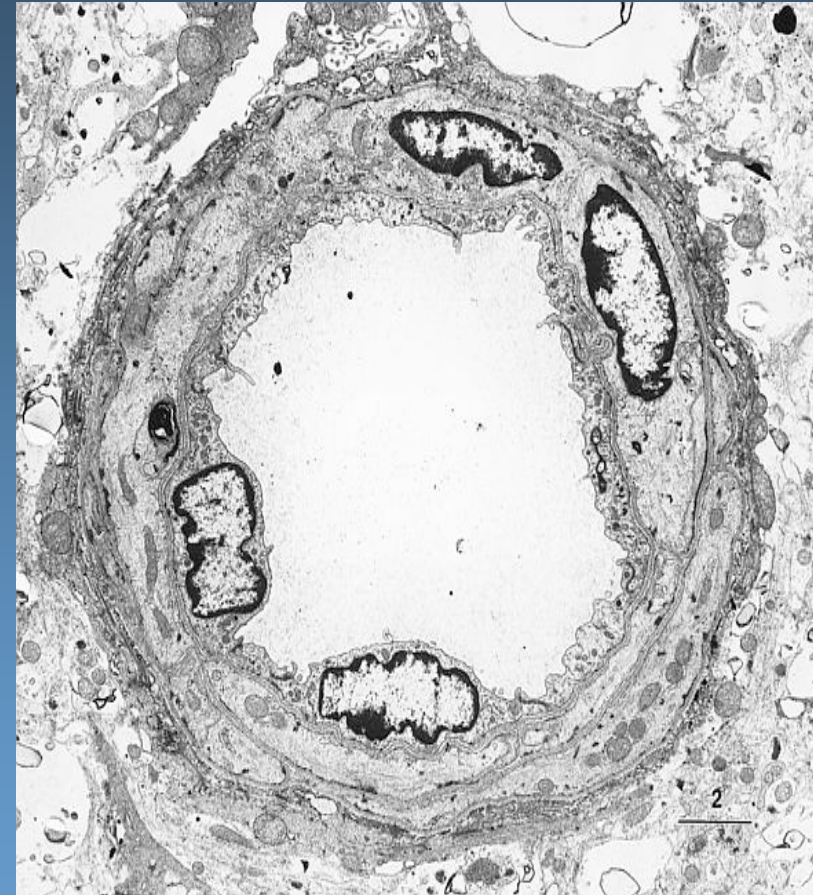
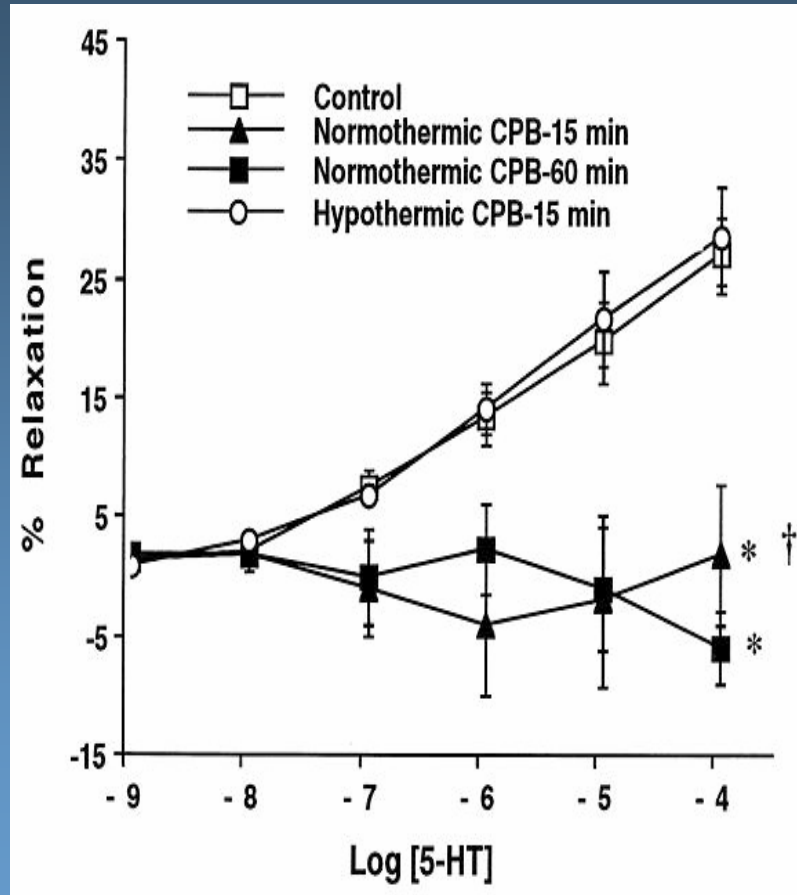
Platelet Administration and Outcomes (Multivariate Logistic Regression Analysis)



Entrapment of Platelets in Ischemic Brain Tissue



Cerebrovascular response to Serotonin post-CPB



*P<0.05 vs control; †p<0.05 vs Hypothermic

Stamler et al, ATS 1996



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C-Reactive protein and inflammatory response associated to neurocognitive decline following cardiac surgery

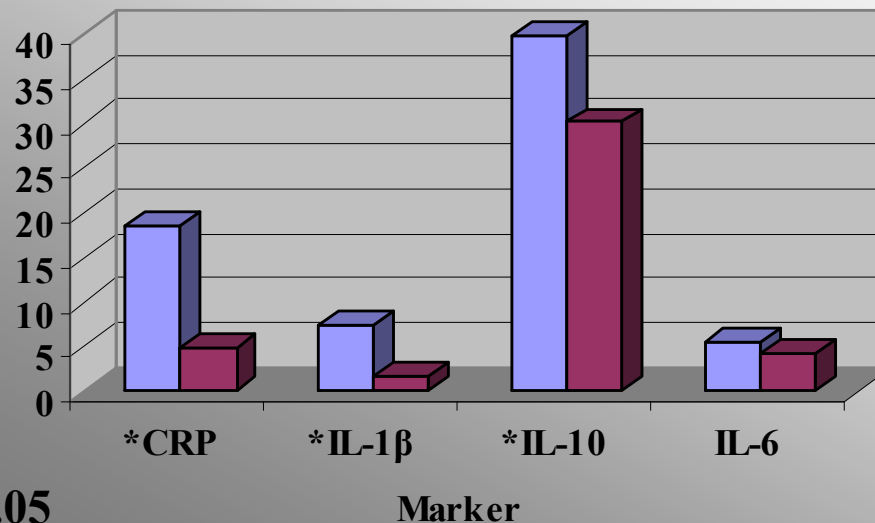
Basel Ramlawi, MD,^a James L. Rudolph, MD,^b Shigetoshi Mieno, MD,^a Jun Feng, MD, PhD,^a Munir Boodhwani, MD,^a Kamal Khabbaz, MD,^a Sue E. Levkoff, ScD,^c Edward R. Marcantonio, MD,^d Cesario Bianchi, MD, PhD,^a and Frank W. Sellke, MD,^a Boston, Mass

Serologic Markers of Brain Injury and Cognitive Function After Cardiopulmonary Bypass

Basel Ramlawi, MD,* James L. Rudolph, MD,†|| Shigetoshi Mieno, MD,* Kamal Khabbaz, MD,* Neel R. Sodha, MD,* Munir Boodhwani, MD,* Sue E. Levkoff, ScD,‡ Edward R. Marcantonio, MD,§ and Frank W. Sellke, MD*

(Ann Surg 2006;244: 593–601)

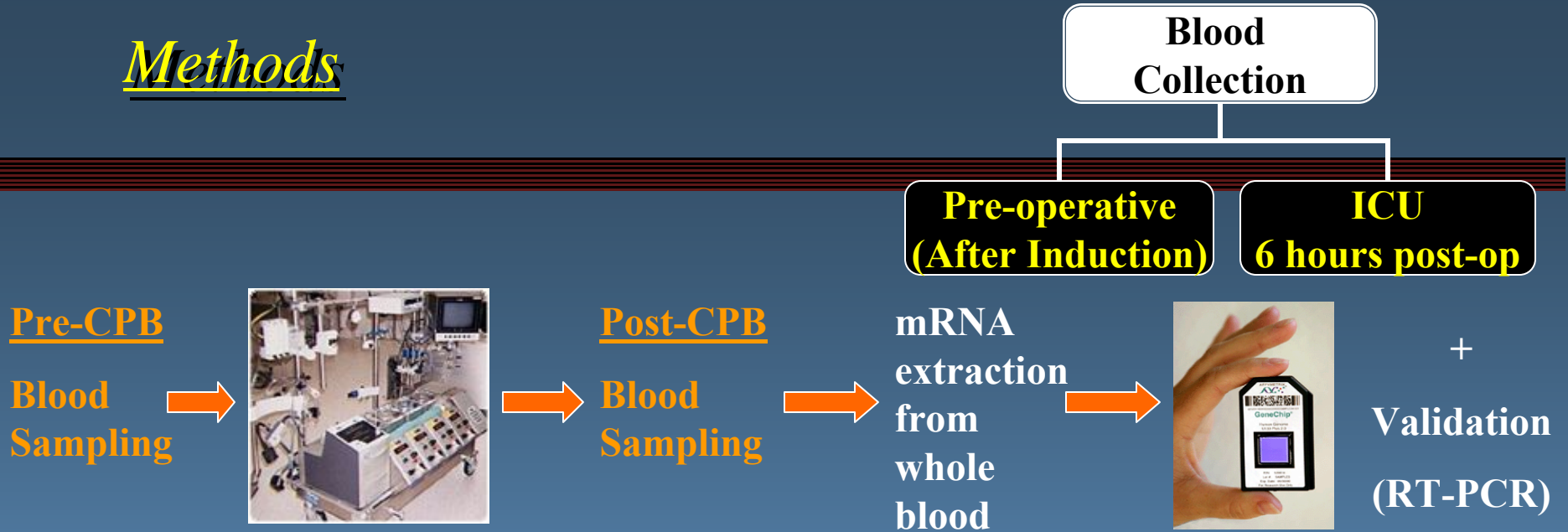
**Mean Fold Change of Inflammatory Markers
(Pre-op vs. 6hrs post-op)**



*p < 0.05

■ NCD ■ No NCD

Methods



- Sample assays were all performed in duplicate via blinded analysis.
→ *Each patient serves as their own control for intra-patient gene expression comparison (pre vs. post).*
- Immediate mRNA stabilization / extraction from whole blood using PAXgene Qiagen system. → *RNA integrity confirmed by gel electrophoresis (A620/A280 ratio 1.7-1.9).*
- Affymetrix GeneChip U133 Plus 2.0 (>40,000 genes).
- Validation of microarray gene expression results.
→ *RT-PCR for a subset of genes.*



Upregulated Genes in NORM Patients

Genetic Pathway

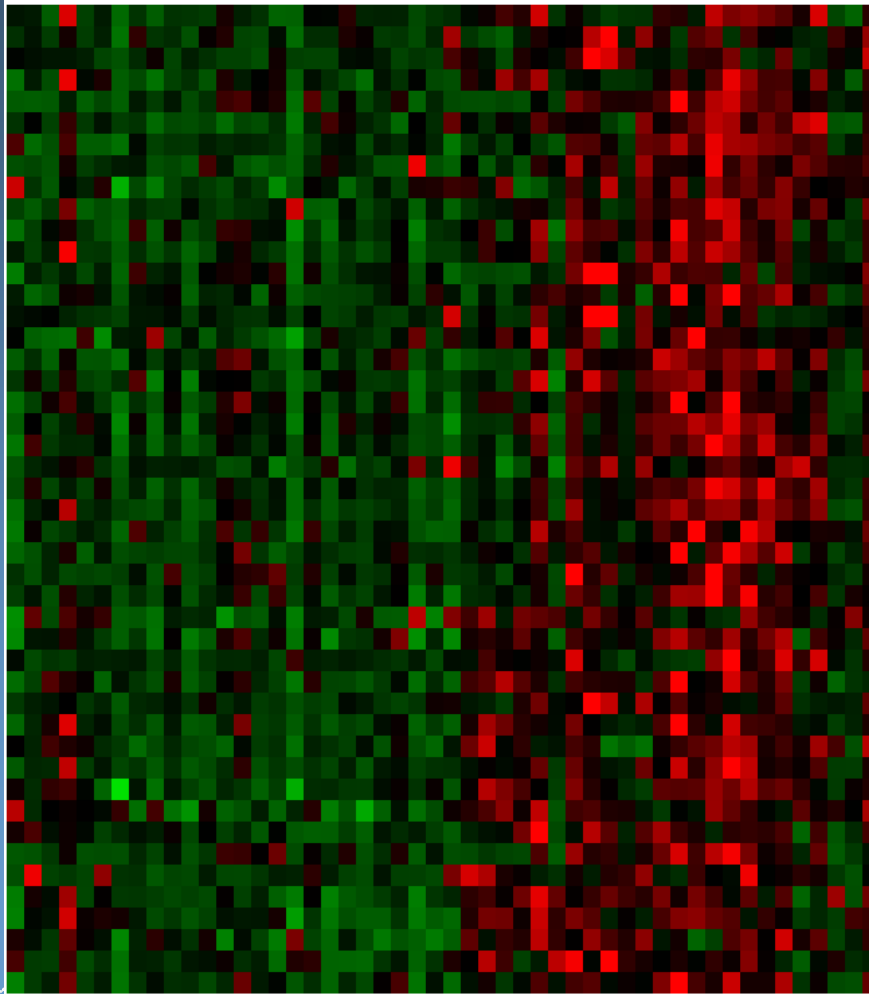


Anti-Apoptosis

Cell Redox
Hemostasis

Fatty-Acid
Betaoxidation

Response to
Stress



- mucosa associated lymphoma translocation gene 1
- Baculoviral IAP repeat-containing 6 (apollon)
- synuclein, alpha (non A4 component of amyloid pre
- mucosa associated lymphoma translocation gene 1
- SON DNA binding protein
- mucosa associated lymphoma translocation gene 1
- forkhead box O1A (rhabdomyosarcoma)
- baculoviral IAP repeat-containing 3
- CASP8 and FADD-like apoptosis regulator
- baculoviral IAP repeat-containing 6 (apollon)
- chromobox homolog 4 (Pc class homolog, Drosophila)
- caspase 2, apoptosis-related cysteine peptidase
- Notch homolog 2 (Drosophila)
- apoptosis inhibitor 5
- insulin-like growth factor 1 receptor
- tumor necrosis factor receptor superfamily, membe
- phosphoprotein enriched in astrocytes 15
- bifunctional apoptosis regulator
- sema domain, immunoglobulin domain (Ig)
- selenoprotein W, 1
- chromosome 11 open reading frame 31
- thioredoxin reductase 3
- chromosome 11 open reading frame 31
- carmitine palmitoyltransferase 1A (liver)
- Acyl-Coenzyme A oxidase 1, palmitoyl
- carmitine palmitoyltransferase II
- choline kinase beta
- HtrA serine peptidase 2
- Hypothetical protein LOC339751
- eukaryotic translation initiation factor 1
- Activating transcription factor 6
- retinoic acid receptor, alpha
- Activating transcription factor 6
- stannin
- Activating transcription factor 6
- nucleophosmin (nucleolar phosphoprotein B23, numa
- mitogen-activated protein kinase 13
- MHC class I polypeptide-related sequence A
- serum/glucocorticoid regulated kinase family, mem
- cisplatin resistance-associated overexpressed pro
- Hypothetical protein LOC339751
- sterile alpha motif and leucine zipper containing
- PTK2B protein tyrosine kinase 2 beta
- thioredoxin domain containing 4 (endoplasmic reti
- sterile alpha motif and leucine zipper containing
- mitogen-activated protein kinase 1

Gene Regulation (6H vs. PRE)	Patient Group	Gene Ontology Pathway	Genes Observed	p-value
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Down

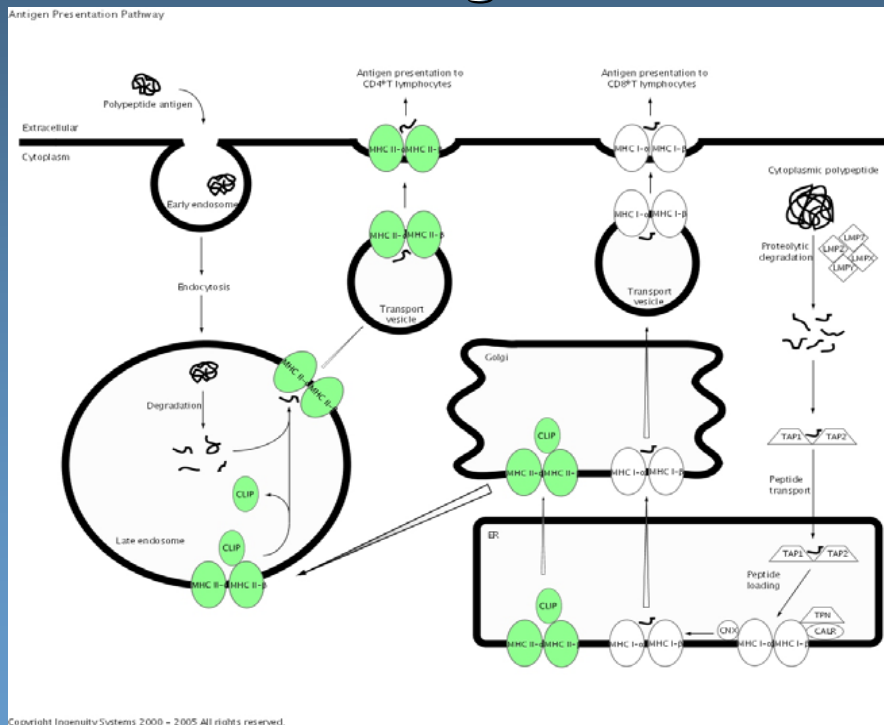
Up



Antigen Presentation Pathway

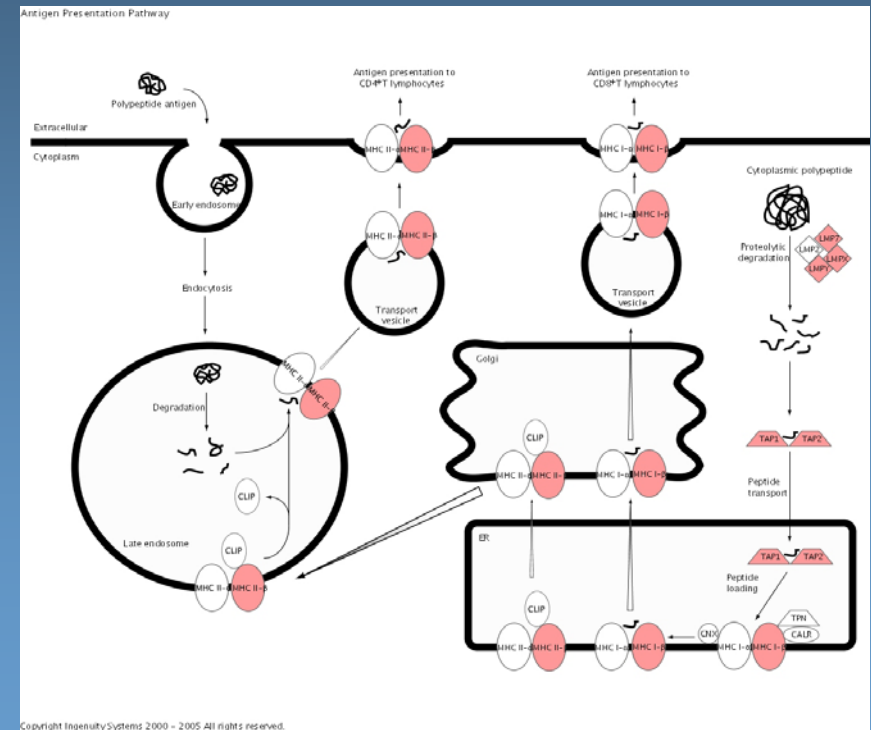
NCD Group

Downregulated



NORM Group

Upregulated



Summary

- Type 2 CNS injury remains a common complication early post-CPB (40%).
- Patients with type II CNS injury have inherent differences in their gene expression response post-CPB.
- Genetic pathways that were differentially expressed include:
 - Inflammation and oxidation homeostasis
 - Immune response, antigen presentation and T cell activation.
 - Anti-Apoptosis / Apoptosis induction
 - Cell-cell adhesion
 - Blood coagulation
- May play a beneficial role for future pre-operative prediction (risk-assessment) or patient-tailored therapy.

Limitations of Study: - Small sample size

- Multiple comparisons



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What can we do to Limit Neurologic Injury after Cardiac Surgery in High Risk Patients?

- Provide optimal cerebral perfusion during surgery
- Limit aortic manipulation
- Provide a quick, good operation
- Pharmacologic interventions (eg, serine protease inhibition) to limit inflammation
- Minimize bleeding
- Maintain tight control of blood sugar
- Appropriate timing of surgery and patient selection

