

CPB与脑损伤

cardiopulmonary bypass and cerebral injury

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CPB的贡献

by John Gibbon in 1953

- u 开心直视手术**
- u 心脏辅助装置**
- u ECOMO**
- u 自体血液回输**
- u 心肺脑复苏抢救**

CBP有待解决的问题

- 异常出血
- 全身炎症反应
- 多器官衰竭
- 神经功能损害
- 永久性智能损害
- 肺功能损害
- 等等

本讲内容提要

- 脑损伤发病率
- 相关危险因素
- 发病原因
- 防治措施

脑损伤发病率

- **Neurologic deficits (type I)** **1-6%**
 - 致命脑损害
 - 脑卒中 **4.8-5.2%**
 - 意识障碍
 - 惊厥
- **Neuropsychologic deficits (type II)** **60-80%(1W)**
 - 认知变化
 - 记忆学习
 - 视觉-运动反应

StephenA Mills: Cerebral injury and cardiac operations. Ann Thorac Surg 1993;56:S86-91

卒中发病率

16,184 cardiac surgery	4.6%
• CABG 8,917 (beating heart 1,842)	3.8% (1.9%)
• aortic valve surgery 1,830	4.8%
• mitral valve surgery 708	8.8%
• double or triple valve surgery 381	9.7%
• CABG and valve surgery 2,506	7.4%

Bucerius,J; Gummert,JF; Borger,MA: Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients. Ann Thorac Surg. 2003 Feb; 75(2): 472-8

脑损伤临床表现

F轻度

意识模糊、手眼协调运动障碍、
眼聚焦不良、视网膜微栓、视野缺陷

F中度

麻醉苏醒延迟、谵妄、妄想、定向力障碍、
躁动、癫痫、手足舞蹈徐动症

F重度

偏瘫、去皮层状态、昏迷

体外循环

心脏直视手术

中枢神经系统

并发症（严重）

外科手术失败

延长住院、增加费用、生活质量降低

心脏术后脑并发症的危险因子

危险因子	Type I 并发症	Type II 并发症
近心端动脉硬化	4.52 [2.52 to 8.09] ^[*]	
神经系统病史	3.19 [1.65 to 6.15]	
使用 IABP	2.60 [1.21 to 5.58]	
糖尿病	2.59 [1.46 to 4.60]	
高血压病史	2.31 [1.20 to 4.47]	
肺疾病史	2.09 [1.14 to 3.85]	2.37 [1.34 to 4.18]
不稳定心绞痛史	1.83 [1.03 to 3.27]	
年龄 (每增加 10 年)	1.75 [1.27 to 2.43]	2.20 [1.60 to 3.02]
入院收缩压 > 180 mm Hg		3.47 [1.41 to 8.55]
酗酒史		2.64 [1.27 to 5.47]
CABG 史		2.18 [1.14 to 4.17]
术日有心律失常		1.97 [1.12 to 3.46]
抗高血压治疗		1.78 [1.02 to 3.10]

CABG = coronary artery bypass graft surgery; IABP = intra-aortic balloon pump.

***Adjusted odds ratio [95% confidence intervals] for type I and type II cerebral outcomes associated with selected risk factors from the Multicenter Study of Perioperative Ischemia.**

Arrowsmith JE, Grocott HP, Reves JG, et al: Central nervous system complications of cardiac surgery. Br J Anaesth 84:378, 2000.

卒中危险因素

CPB血液稀释？

- **10949例CPB病人，1999-2004年，4所医院**
- **考察Stroke发生，术后30d**
- **Multivariable logistic regression analysis**
- **Hb与stroke的关系**
- **CPB中最低Hb值是独立危险因子**
- **Hb每下降1%，Odds ratio上升10%，P=0.002**
- **是否为因果关系？**

Karkouti,K; Djaiani,G; Borger,MA: Low hematocrit during cardiopulmonary bypass is associated with increased risk of perioperative stroke in cardiac surgery. Ann Thorac Surg 2005 Oct; 80(4): 1381-7

卒中危险因素 术后房颤

- **2630例CPB下CABG，术后卒中率2%（52例）**
- **卒中后死亡23.1%（12例）**
- **36.5%（19例）卒中前有房颤，平均2.5次，6d内**
- **在房颤发生平均21.3h后，发生卒中**
- **结论：房颤是卒中的危险因素**

Lahtinen,J; Biancari,F; Salmela,E: Postoperative atrial fibrillation is a major cause of stroke after on-pump coronary artery bypass surgery. Ann Thorac Surg 2004 Apr; 77(4): 1241-4

Murdock,DK; Rengel,LR; Schlund,A: Stroke and atrial fibrillation following cardiac surgery. WMJ. 2003; 102(4): 26-30

Off pump的卒中率较低

- 脱泵搭桥vs CPB

	研究数量	病人数	odds ratio	95%CI	P
Stroke	38	34126	0.55	0.34-0.69	0.0000006

- 减少了脑卒中的发生

James T Raston, Stephen J Tregear, Charles M Turkelson: Meta-Analysis of short-term and mid-term outcomes following off-pump coronary artery bypass grafting. Ann Thorac Surg 2003; 76:1510-5

CPB搭桥卒中率较高

- 10573病人行CABG， 2%卒中

On-pump

Off-pump

173 (80%)

44 (20%)

时间 2d

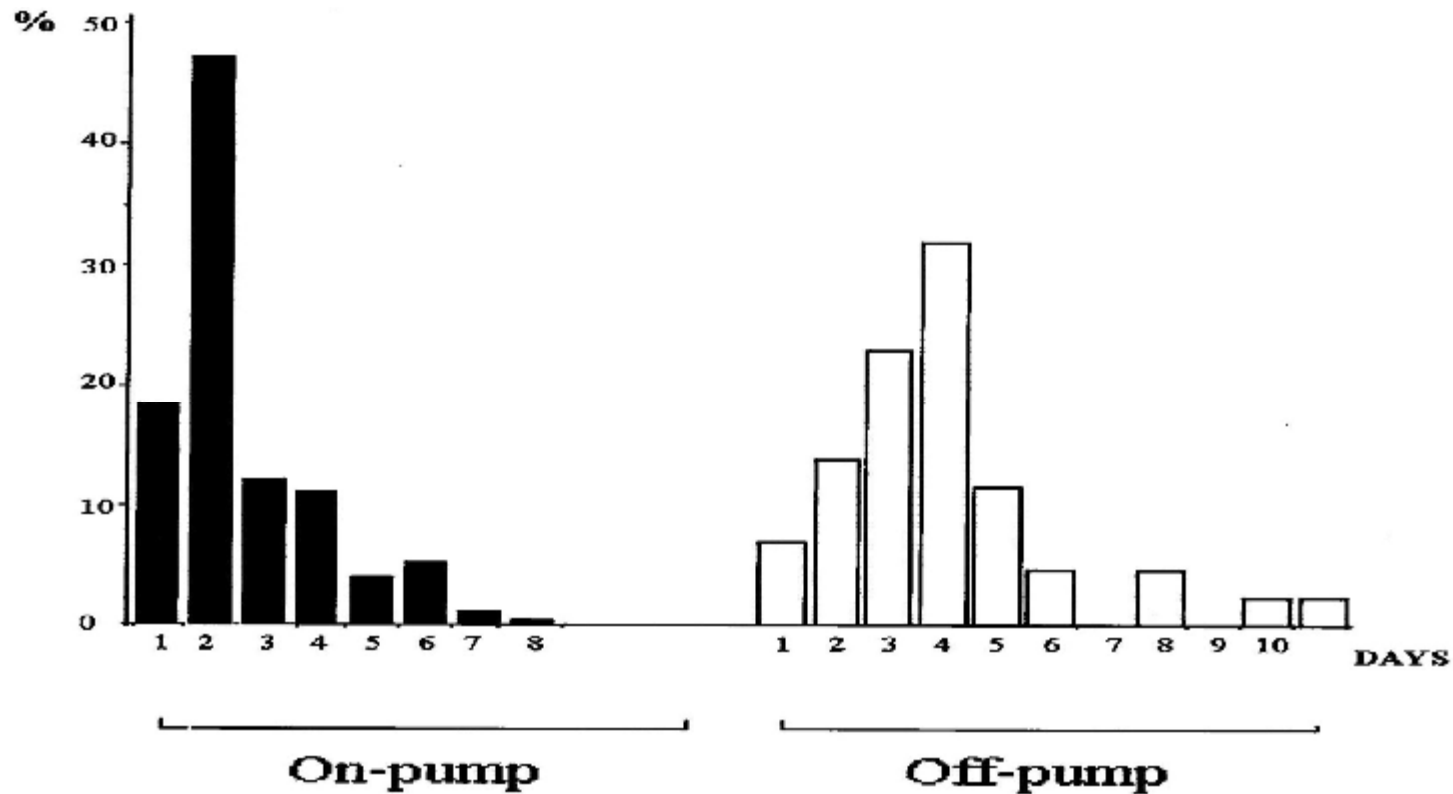
4d

Odds 5.3 (95%CI: 2.6-10.9; $p < 0.01$)

- 结论: On-pump的stroke发生率高，出现早，两者的发生机制不同

Peel,GK; Stamou,SC; Dullum,MK: Chronologic distribution of stroke after minimally invasive versus conventional coronary artery bypass. J Am Coll Cardiol. 2004 Mar 3; 43(5): 752-6

术后脑卒中发生时间的分布



脑损伤原因

- CPB

栓塞 微栓子 (<200 μ m: 气栓、脂质粒子、血栓、粒子
(粥样硬化斑块脱落物、钙斑块脱落物))

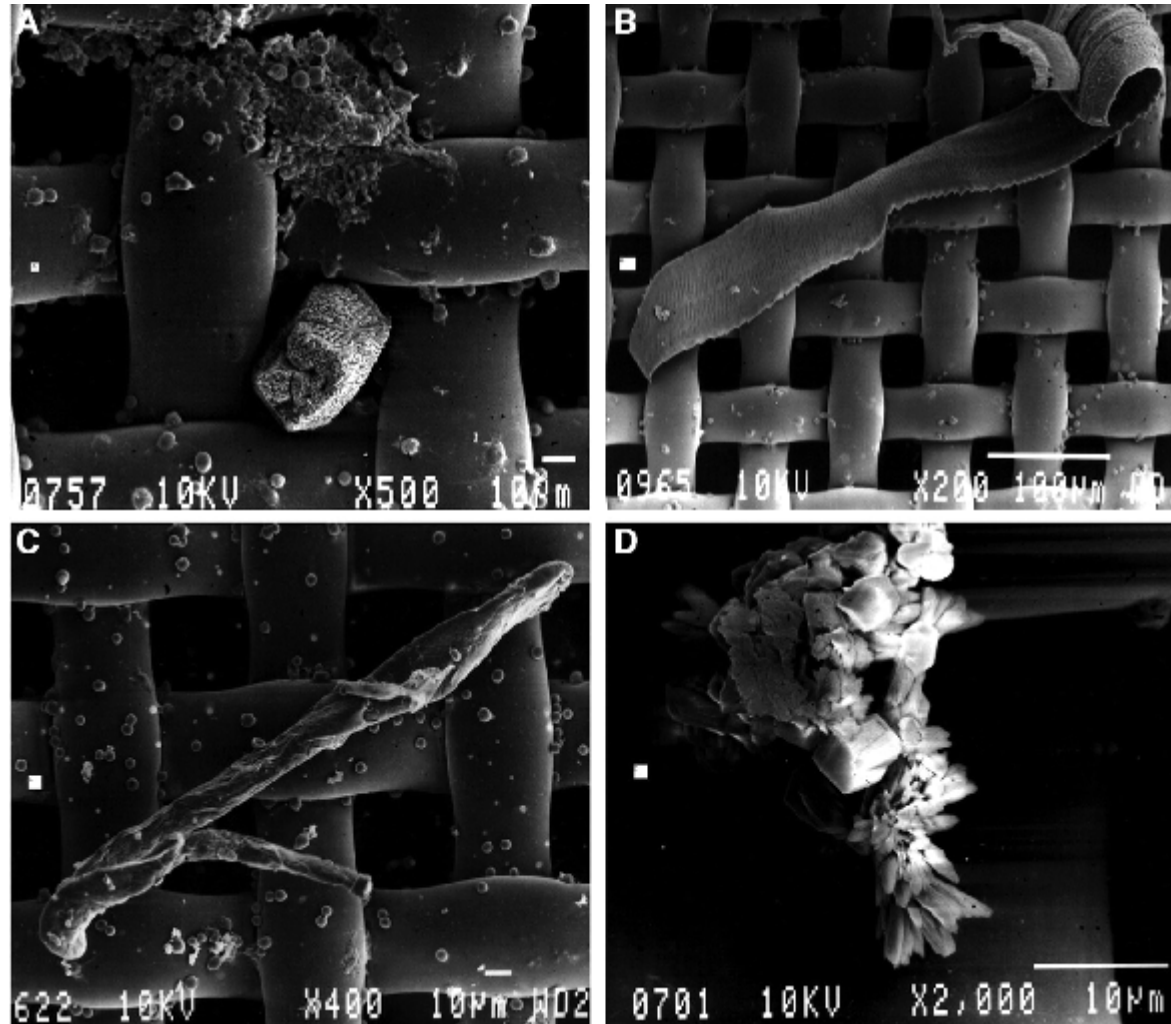
低灌注、再灌注损伤 (动脉硬化)

炎症反应 (管道组织不相容)

应激反应

- 脑水肿
- 脑高温
- 遗传基因多态性: 载脂蛋白、炎症反应等

Figure 2. Scanning electron micrographs of 40-micron arterial line filters after clinically uneventful cardiopulmonary bypass



Hogue, C. W. et al. *Anesth Analg* 2006;103:21-37

- A) 阻隔了大块水晶状物. 附着红细胞的纤维蛋白团块. B) 脱落的硅橡胶颗粒 (80 x 600 um)
C) 外源有机纤维颗粒. D) 晶体沉积复合物.

Neurocognitive Function and Cerebral Emboli: Randomized Study of On-Pump Versus Off-Pump Coronary Artery Bypass Surgery

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FRCP, Juan Carlos Kaski, MD, DSc, and Marjan Jahangiri, FRCS

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Sciences, University of York, York, United Kingdom

Ann Thorac Surg 2007;83:475–82

研究目的

比较**CPB**和脱泵冠脉搭桥手术病人

- 术后神经认知功能
- 脑血栓

方法

共212病人，

CPB: 104; 脱泵: 108

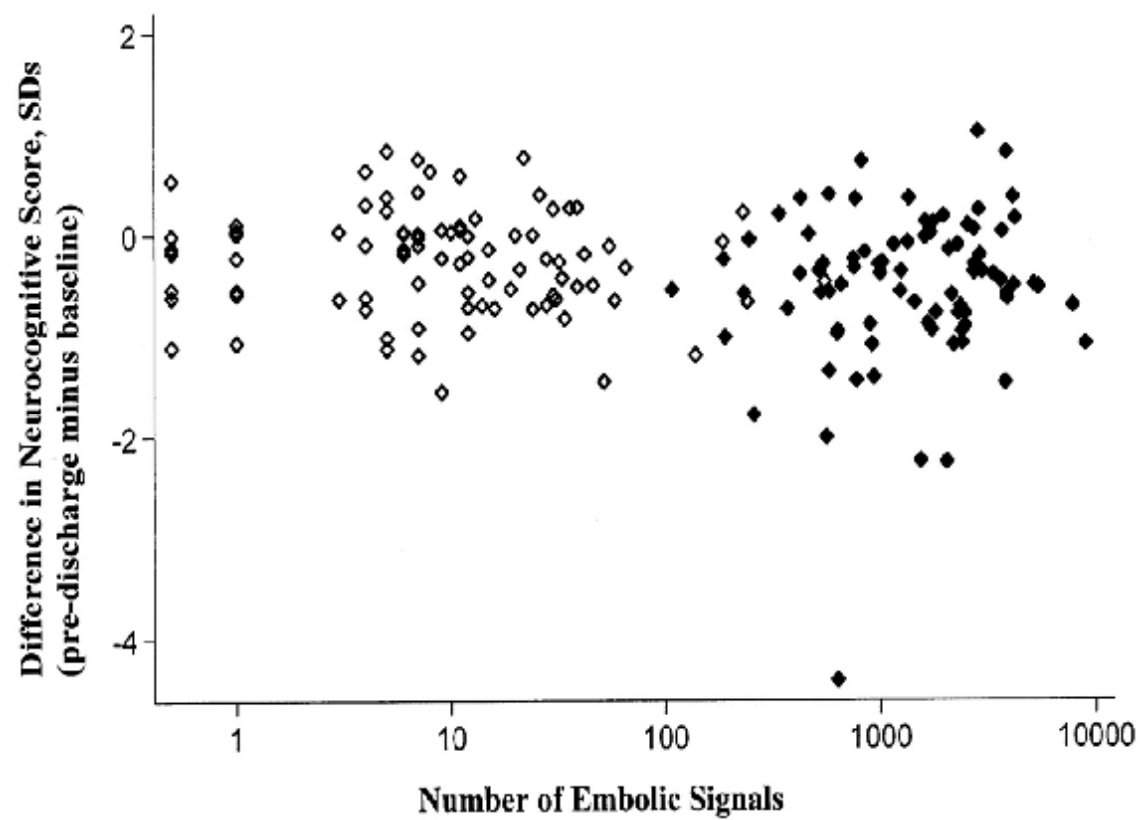
双侧经颅多普勒超声MCA，探测栓子

认知功能测定：术前、出院、术后6周、术后6月

结果

	CPB	Off-pump
栓子信号	1605 (751, 2473)	9 (4, 27)

认知功能：出院时**CPB**组差于**Off-pump** (**P=0.01**)，但以后的测定未显示差别。



术前和出院时认知功能的变化与栓子信号的关系。
实心符号：CPB组；空心符号：Off-pump

结论

- p 栓子在CPB较多
- p Off-pump组在出院时认知功能较好，可能与栓子较少有关
- p 但在术后6周以后，认知功能就没有差别

应激反应与认知功能

应 激 ① 糖皮质激素 ②

糖皮质激素受体 ③ 认知功能障
碍
(额叶 海马)

载脂蛋白E与认知功能

ApoE (2、3、4)

脑内脂转运

胆固醇代谢

b-淀粉样蛋白 代谢 转运 沉积

CNS 生长发育 功能维持 伤后修复

ApoE ε 4是认知功能障碍的危险因素

载脂蛋白E与认知功能

ApoE ϵ 4 与淀粉样b-肽紧密结合

b-淀粉样蛋白代谢 清除障碍

b-淀粉样蛋白沉积

老年痴呆

术后认知功能障碍

褪黑激素melatonin

- 松果体 光线 节律性分泌 睡眠
- 自由基清除 抗氧化活性
- 神经免疫调节

基因表达与认知功能损害

Genomic expression pathways associated with brain injury after cardiopulmonary bypass

By Basel Ramlawi, MD,^a Hasan Otu, PhD,^b James L. Rudolph, MD,^e Shigetoshi Mieno, MD,^a Isaac S. Kohane, MD, PhD,^c Handan Can, PhD,^b Towia A. Libermann, PhD,^b Edward R. Marcantonio, MD,^d Cesario Bianchi, MD, PhD,^a and Frank W. Sellke, MD^a

J Thorac Cardiovasc Surg 2007;134:996-1005

方法

- **42例病人，CABG、瓣膜手术**
- **检测术前、后认知功能**
- **发现neurocognitive decline (17/42 [40.5%] patients)**
- **分成NCD组、正常组（NORM组）**
- **基因芯片**
- **全血mRNA**

结果

	NCD组	NORM组
Upregulated基因	531	2214
Downregulated基因	670	580

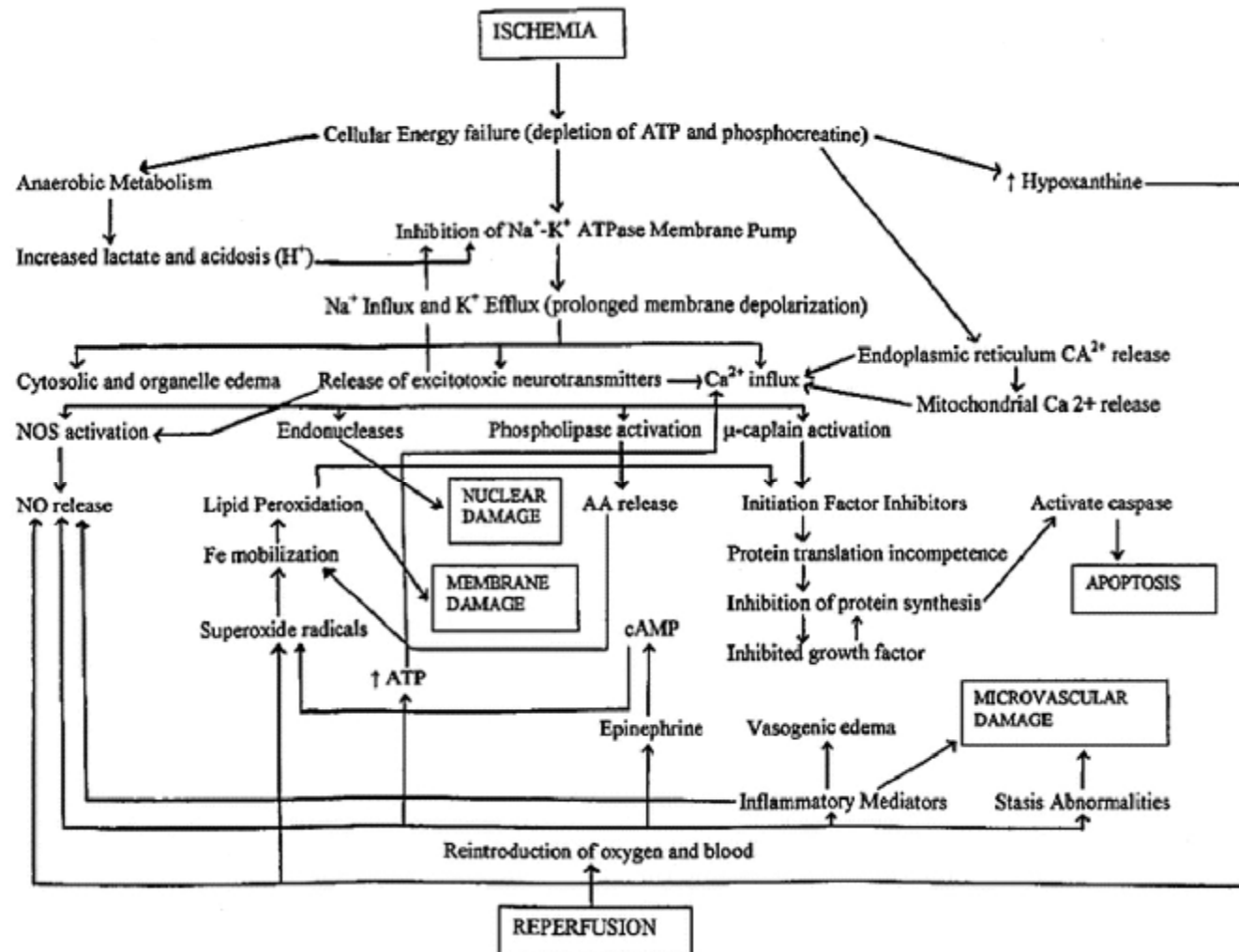
两组间基因表达有明显差异，最大不同体现在**NCD**病人炎性基因(包括**FAS, IL2RB, CD59**)、抗原表达基因(包括**HLA-DQ1, TAP1, TAP2**)、细胞粘附基因(包括**ICAM2, ICAM3, CAD7**)

▪

缺血脑损伤的机制

- § ATP耗竭
- § 细胞膜通透性 (H_2O 、 Na^+ 、 Ca^{2+}) -
- § 前列腺素生成
- § 自由基生成
- § 乳酸蓄积
- § 葡萄糖加重脑缺血损伤
- § NO-NMDA高反应性

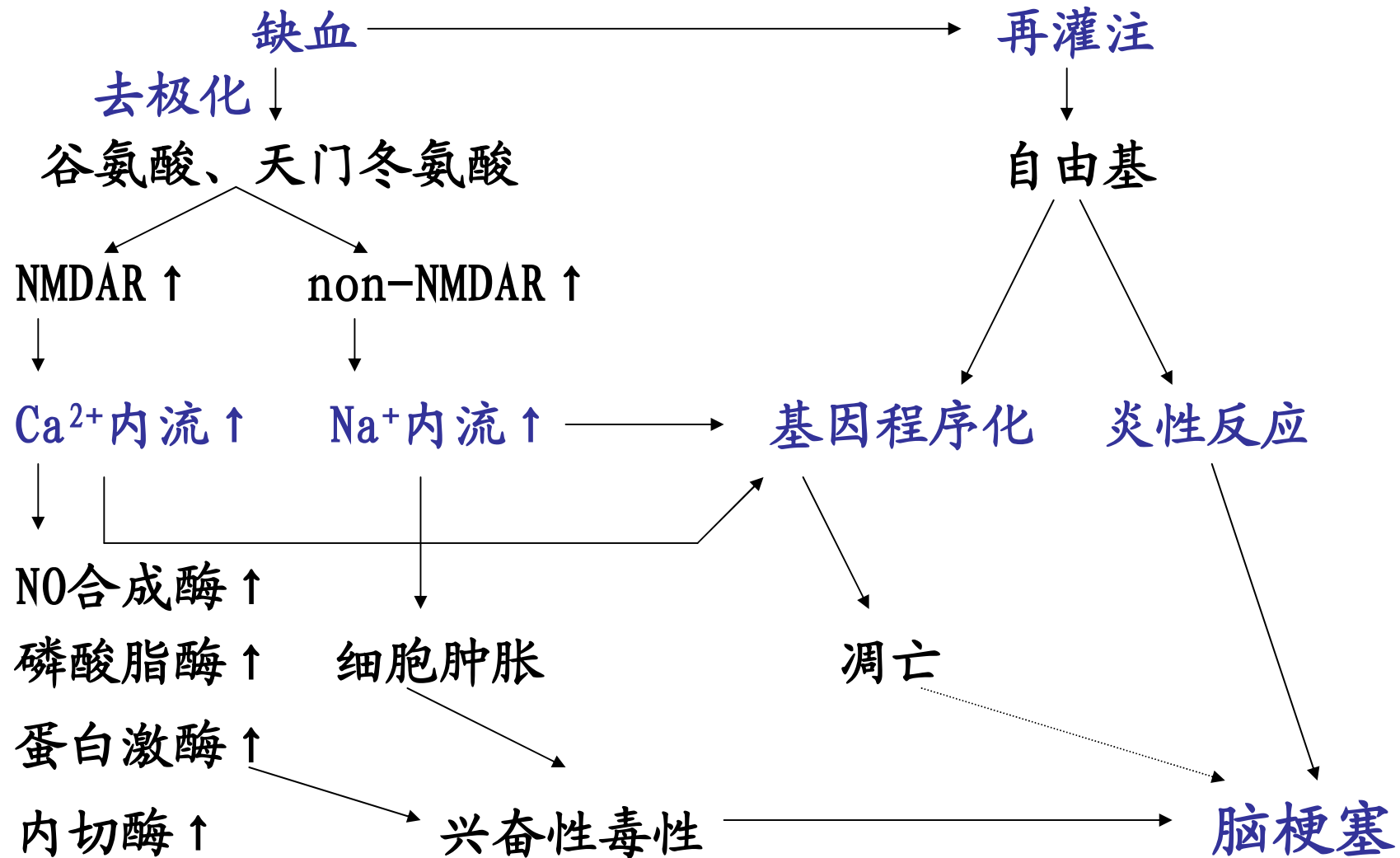
脑缺血再灌注损伤的复杂生化和分子通路



Hogue, C. W. et al. Anesth Analg 2006;103:21-37

ANESTHESIA & ANALGESIA

缺血神经元兴奋性毒性



脑损伤化学标志物

- 肌酐磷酸激酶(**CK-BB**) 动脉和颈内静脉差
- 乳酸 动脉和颈内静脉差
- 腺苷激酶 (**adenylkinase**)
- 神经原特异烯醇酶 (**NSE**)
- **S-100**蛋白
- 髓鞘碱性蛋白
- 乳酸脱氢酶

防治措施

一、技术

外科

灌注

《 麻醉

二、 药物

心脏外科技术

- 选择病人
- 动脉桥
- 深低温、停循环
- 阻断一次
- 心内排气
- 心肌逆灌 栓塞

升主动脉硬化处理措施

- 血管超声引导，操作避开硬化斑块
- 避免部分夹闭主动脉，采用单次全夹闭
- 乳内动脉近端搭桥（Y型）吻合，避免主动脉操作
- 采用腋动脉、无名动脉、主动脉弓远端置管行**CPB**，避免升主动脉置管
- 改良主动脉插管：低流速型、内置滤器、**7cm**长
- 采用脱泵搭桥，Y型吻合
- 深低温停循环，更换主动脉弓（严重硬化）

对于有**颈、脑血管病**的病人，采用
脱泵搭桥可以杜绝脑卒中的发生

Yaku,H; Doi,K: Off-pump coronary artery bypass via median sternotomy. Kyobu-Geka. 2006 Jul; 59(8 Suppl): 607-13

对于有**外周血管病**的病人，采用脱
泵搭桥可以减少脑卒中的发生

Keenan,DJ; Pullan,DM; Dihmis,WC: Coronary surgery in patients with peripheral vascular disease: effect of avoiding cardiopulmonary bypass. Ann Thorac Surg. 2004 Apr; 77(4): 1245-9

脱泵搭桥使神经事件显著下降

	CBP	Off-pump
人数	2002	738
发生率	2.1%	0.9%
Odd ratio	2.6 (1.2-5.9)	

Zangrillo,A; Crescenzi,G; Landoni,G: Off-pump coronary artery bypass grafting reduces postoperative neurologic complications.

J Cardiothorac Vasc Anesth. 2005 Apr; 19(2): 193-6

Sharony,-R; Grossi,EA; Saunders,PC: Propensity case-matched analysis of off-pump coronary artery bypass grafting in patients with atheromatous aortic disease. J Thorac Cardiovasc Surg. 2004 Feb; 127(2): 406-13

**A组：仅有病史者做多普勒，心脏术中(CPB)
行CEA； 58/627人**

**B组：术前常规行多普勒超声检查颈动脉和在
做心脏手术前行CEA； 90/761人**

结果：	A	B
卒中率	24/627 (3.82%)	2/761 (0.26%) (p<0.001)
卒中死亡率	12/627(1.91%)	0/761 (p<0.001)

**结论： 常规多普勒检查，术前局麻行CEA，
可以有效降低术后脑卒中**

De Feo,M; Renzulli,A; Onorati,F: The risk of stroke following CABG: one possible strategy to reduce it?

Int J Cardiol. 2005 Feb 15; 98(2): 261-6

主动脉近端硬化斑块

确诊方法

- 术前**MR**血管造影
- 术中血管多普勒超声
(正常主动脉内膜厚度 $\leq 3\text{mm}$)

处理

- 脱泵搭桥

Djaiani,GN: Aortic arch atheroma: stroke reduction in cardiac surgical patients. Semin-Cardiothorac-Vasc-Anesth. 2006 Jun; 10(2): 143-57

灌注技术

- 灌注压适宜 50-100mmHg CPB开始时
- 膜肺优于鼓泡肺
- 动脉滤器 20-40mm
- pH管理
- 复温 温度（缓慢、均匀）
- 搏动灌注

CPB心脏手术后神经并发症与pH管理的影响 前瞻性随机临床研究

Table 3. Prospectively Randomized Clinical Trials of the Effects of Acid-Base Management During CPB on Neurologic Complications After Cardiac Surgery

Study	n	Findings
Murkin et al (134)	316	Frequency of cognitive impairment no different between α -stat and pH-stat management using primary endpoints. Subsequent analysis suggested a benefit with α -stat when CPB duration >90 min ($P = 0.047$ versus pH-stat). Whether there was correction for multiple comparisons is not clearly stated.
Bashein et al (154)	86	No difference in psychometric endpoints 7 mo after CABG surgery for patients undergoing CPB with α -stat or pH-stat management.
Stephan et al (155)	65	Neurologic deficits (mostly cerebellar and cranial nerve deficits) more common 7 days after surgery with pH-stat versus α -stat management. Psychometric testing was not performed and long-term results were not reported.
Patel et al (156)	70	Frequency of cognitive dysfunction 6 wk after CABG surgery was not different between groups undergoing CPB with pH-stat versus α -stat management using predefined endpoints. Patients with cerebrovascular disease or diabetes were excluded from study. A benefit of α -stat management was found when the definition of cognitive decline was changed during <i>post hoc</i> data analysis from >2 SD decline from baseline on >2 tests to decline on >3 tests.

CPB = cardiopulmonary bypass; CABG = coronary artery bypass graft.

Hogue, C. W. et al. *Anesth Analg* 2006;103:21-37

ANESTHESIA & ANALGESIA

血气管理

pH-stat vs. alpha-stat

pH-stat 优于 alpha-stat

在小儿或深低温停循环、低灌流

因为：

ü CBF 增加

ü CMRO₂ 下降

ü p_{Hi} 更快恢复

ü 细胞外 pH 较低更符合小儿生理

pH-stat = alpha-stat

在成人或中、浅低温

但 alpha-stat 更简便易行

Optimal blood gas management during deep hypothermic paediatric cardiac surgery: alpha-stat is easy, but pH-stat may be preferable. Paediatric Anaesthesia 2002;12:199-204

体外循环心脏直视手术中 中枢神经系统的监测

食道超声

微栓数量、时间

经颅多普勒

微栓数量、时间

脑电图

脑血流量

颈静脉球部血氧饱和度 $> 50\%$ (**17%-23%!**)

脑血氧饱和度 (近红外光谱仪)

Monitoring Brain Oxygen Saturation During Coronary Bypass Surgery: A Randomized, Prospective Study

Department of Anesthesiology and Perioperative Medicine; Clinical
Perfusion Services; and Division of Cardiac Surgery, University Hospital-
LHSC, University of Western Ontario, London, Ontario, Canada.

Anesth Analg 2007;104:51-58

脑氧合监测对预后有益吗？

研究设计

	对照组	干预组
病例数	100	100
监测rS02	不干预	干预使>75%

观察指标：术后30d内不良事件（新发心梗、IABP、CVA、纵隔炎、脓毒症、伤口感染、机械通气时间 $>24\text{ h}$ 和 $>48\text{ h}$ 、须治疗的心律失常、出血再次手术、肾衰透析、胸骨裂开、术后7天未能出院、术后30天再入院）

干预包括：头正中位，颜面无充血，使 $\text{PaCO}_2 > 40\text{ mmHg}$ ，使 $\text{MAP} > 60\text{ mmHg}$ ，使CI达到 $2.5\text{ L/m}^2/\text{min}$ ，提高 FiO_2 ，使HCT达到20%

Table 1. Preoperative Demographic and Morphometric Data

	Control (<i>n</i> = 100)	Intervention (<i>n</i> = 100)	<i>P</i> -value
Age (yr)	61.8 ± 10.3	61.8 ± 9.3	0.95
Age >70 yr	24	24	1.0
Age >80 yr	1	1	1.0
Gender (male/ female)	88/12	87/13	0.83
BMI	29.7 ± 5.9	29.5 ± 4.2	0.79
CCS angina score	3.17 ± 0.54	3.05 ± 0.67	0.17
Grade of ventricle	1.56 ± 0.84	1.43 ± 0.64	0.24
Grade III or IV ventricle	13	8	0.25
Recent MI	5	5	1.0
CHF	2	4	0.34
Type II DM (non-insulin)	21	21	1.0
Type II DM (insulin)	7	8	0.79
Renal insufficiency	5	12	0.08
TIA	5	1	0.11
CVA	7	7	1.0
COPD	19	16	0.58

BMI is Body mass index; CCS is Canadian Cardiovascular Society angina score from 0 to 4 where increasing grade reflects increased severity of anginal symptoms; Grade of ventricle is a qualitative categorical clinical estimate of global ventricular function from I to IV where increasing grade reflects increased severity of left ventricular (LV) dysfunction; Recent MI is myocardial infarction <30 d of acceptance for surgery; CHF is diagnosis of congestive heart failure; Type II DM (non-insulin) is diagnosis of non-insulin-dependent diabetes mellitus; Type II DM (insulin) is diabetes mellitus chronically treated with insulin; Renal insufficiency is serum creatinine >120 mg/L; TIA is history of transient ischemic attack; CVA is history of cerebrovascular accident; COPD is history of chronic obstructive pulmonary disease.

Table 2. Perioperative Variables and Cerebral Oximetry Parameters

	Control	Intervention	P-value*
Concomitant procedures	4	2	0.68
OPCAB	8	5	0.568
Number of grafts	2.94 ± 0.83	3.12 ± 0.95	0.153
CPB (min)	87.7 ± 65.2	88.7 ± 38.7	0.897
Clamp-time (min)	57.4 ± 23.5	59.4 ± 23.2	0.560
Single clamp (n)	48	58	0.16
Hct (%)	23.8 ± 3.4	24.3 ± 3.2	0.354
Hct <20% (n)	8	4	0.37
Aprotinin (n)	69	83	0.031
pRBC (n)	10	8	0.805
pRBC (units/pt)	3.4 ± 3.8	2.9 ± 1.6	0.365
Phenylephrine (n)	81	89	0.165
Phenylephrine (µg)	2616 ± 2194	2852 ± 2205	0.657
Ventilation time (h)	14.7 ± 23.3	11.4 ± 9.3	0.113
ICU duration (d)	1.87 ± 2.67	1.25 ± 0.84	0.029
ICU >2 d (n)	12	5	0.081
ICU >5 d (n)	4	1	0.211
LOS (d)	6.9 ± 5.5	6.1 ± 4.4	0.294
LOS ≥7 d (n)	29	19	0.099
LOS ≥10 d (n)	14	6	0.063
rSO ₂ baseline	68.9 ± 7.2	70.3 ± 7.1	0.188
rSO ₂ mean	63.4 ± 6.5	63.6 ± 6.9	0.858
rSO ₂ minimum	46.9 ± 7.2	45.1 ± 8.7	0.134
rSO ₂ AUC <75% baseline	117.5 ± 293.7	100.9 ± 134.2	0.148
rSO ₂ AUC <40% baseline	6.72 ± 24.8	5.5 ± 20.8	0.240
rSO ₂ AUC <70% baseline >150%min (n)	6 (6%)	0 (0%)	0.014

Concomitant Procedures are patients in whom an additional procedure was performed coincident with coronary revascularization; OPCAB is off-pump coronary artery bypass surgery; Hct is the mean lowest cardiopulmonary bypass (CPB) hematocrit; Hct <20% is patients with Hct <20% during CPB; Aprotinin is patients receiving 2 m KU aprotinin during CPB; pRBC is patients receiving one or more units packed red blood cells; Phenylephrine is the number of patients administered on CPB; Single clamp is cross-clamp without subsequent partial aortic clamp; rSO₂ is regional oxygen saturation; AUC is area under curve of cumulative rSO₂ values <threshold; ICU is intensive care unit; LOS is length of stay.

* P-value reflects results of t-test, Wilcoxon's rank sum, or Fisher's exact test.

Table 3. Intent-to-Treat 30-D Postoperative Morbidity and Mortality

	Control (<i>n</i> = 100)	Intervention (<i>n</i> = 100)	<i>P</i> -value
Myocardial infarction	3	1	0.62
Use of IABP	4	3	1.0
New onset stroke ^a	4	1	0.368
Mediastinitis ^a	1	0	0.50
Septicemia	1	0	0.50
Wound infection	8	7	1.0
Ventilatory time >24 h	10	3	0.082
Arrhythmia requiring treatment	2	0	0.497
Reoperation for bleeding ^a	1	1	1.0
Surgical reintervention ^a	1	0	0.50
Renal failure requiring dialysis ^a	0	0	
>7 d Duration of postoperative hospitalization	18	11	0.227
Readmission to hospital within 30 d	5	8	0.567
Death ^a	1	0	0.50
Sternal infection	7	5	0.767
Ventilatory time >48 h ^a	4	1	0.368
Patients with ≥1 complication (<i>n</i>)	30	23	0.336
MOMM (<i>n</i>) ^a	11	3	0.048
MOMM >1 (<i>n</i>) ^a	1	0	1.0

MOMM is major organ morbidity and mortality as derived from Society of Thoracic Surgeons database analysis (1) comprised of variables denoted with ^a; MOMM >1 is number of patients experiencing more than one MOMM event; IABP is intraaortic balloon pump.

Table 4. Coronary Bypass Only, 30-d Postoperative Morbidity and Mortality

	Control (<i>n</i> = 96)	Intervention (<i>n</i> = 98)	<i>P</i> -value
Myocardial infarction	3	1	0.365
Use of IABP	3	2	0.680
New onset stroke ^a	4	1	0.209
Mediastinitis ^a	1	0	0.495
Septicemia	0	0	
Wound infection	7	7	1.0
Ventilatory time >24 h	8	2	0.056
Arrhythmia requiring treatment	2	0	0.243
Reoperation for bleeding ^a	1	1	1.0
Surgical reintervention ^a	1	0	0.495
Renal failure requiring dialysis ^a	0	0	
>7 d Duration of postoperative hospitalization	16	10	0.210
Readmission to hospital within 30 d	4	8	0.373
Death ^a	0	0	
Sternal infection	6	5	0.766
Ventilatory time >48 h ^a	4	0	0.058
Patients with ≥ 1 complication (<i>n</i>)	26	22	0.507
MOMM (<i>n</i>) ^a	10	2	0.017

MOMM is major organ morbidity and mortality as derived from the Society of Thoracic Surgeons database analysis (1) comprised of variables denoted with ^a; IABP is intraaortic balloon pump.

Table 5. Type of Cerebral Regional Oxygen Saturation (rSO₂) Interventions in the Intervention Group

Intervention	No. of patients	% Efficacy
Raise pump flow	39	67
Raise MAP	42	62
Normalize Paco ₂	34	50
Deepen anesthesia	27	48
Increase Fio ₂	28	43
Pulsatile perfusion	6	17

No. of patients indicates those patients in whom a specific intervention was undertaken; % Efficacy indicates those instances in whom the intervention was successful in restoring rSO₂. For some patients multiple interventions were used at various intervals such that No. of patients is larger than the Intervention group total. MAP is mean arterial blood pressure.

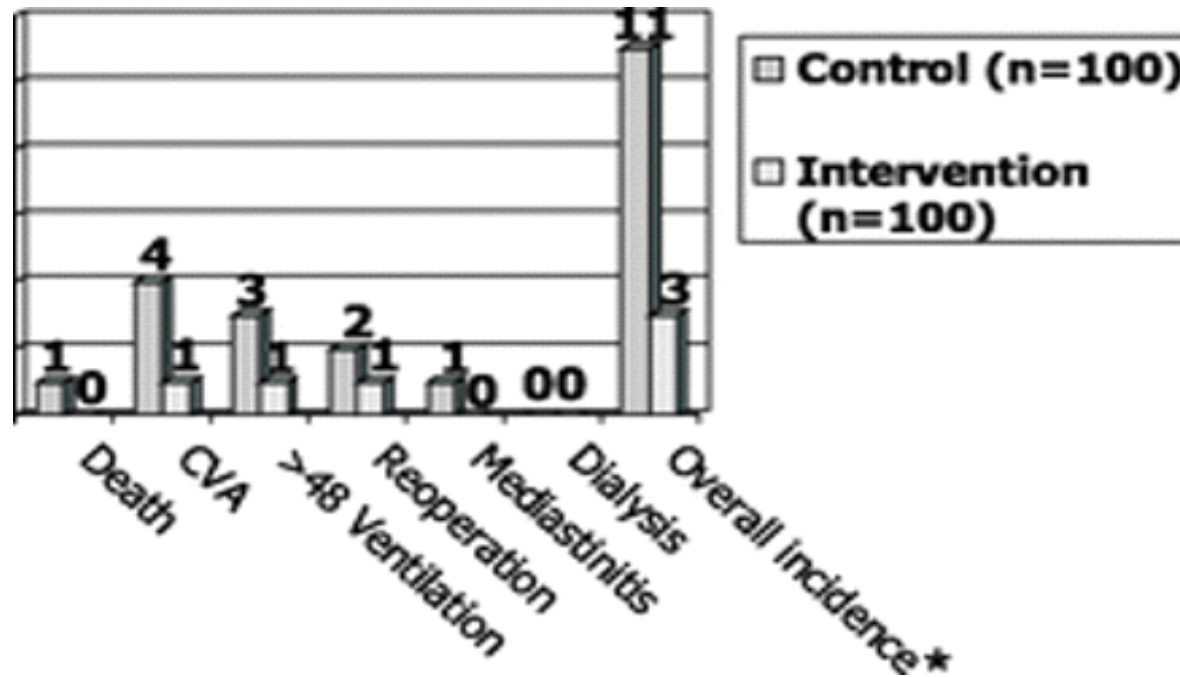


Figure 1. 术后30天死亡和主要器官障碍

CVA is cerebrovascular accident; >48 Ventilation is patients ventilated postoperatively for >48 h. *Overall incidence: $P = 0.048$.

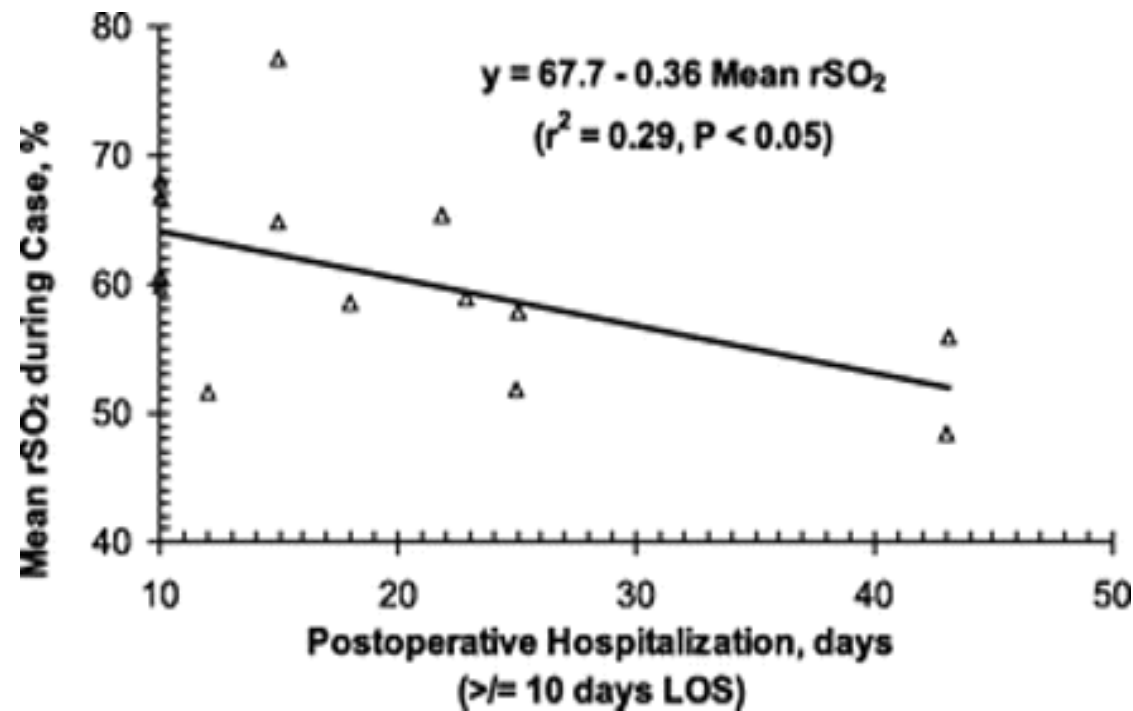


Figure 2. LOS is postoperative length of stay. rSO₂ is regional cerebral oxygen saturation. Linear regression analysis of mean intraoperative rSO₂ in patients with prolonged hospitalization of 10 or more days demonstrating a correlation between lower values of rSO₂ and increased duration of prolonged hospitalization.

文章结论

在CABG术中监测脑 rSO_2 可以避免脑氧饱和度下降

而且能显著降低重要器官衰竭的发生。

RESEARCH ARTICLE

Open Access

Postoperative cognitive deficit after cardiopulmonary bypass with preserved cerebral oxygenation: a prospective observational pilot study

Axel Fudickar*, Sönke Peters, Claudia Stapelfeldt, Götz Serocki, Jörn Leiendecker, Patrick Meybohm, Markus Steinfath, Berthold Bein

研究设计

- 心脏手术**35**例（**CPB**）监测**cSO₂**
- **cSO₂**保持在基础值的**80%**以上（麻醉时）或**55%**以上（**CPB**时）
- 术前、术后**5**天测定**POCD**值
- 测定值下降超过基础值 **20%**诊断为**POCD**
- **POCD**与**lowest cSO₂**的相关性
- **cSO₂** 导致**POCD**的阈值（**threshold**）

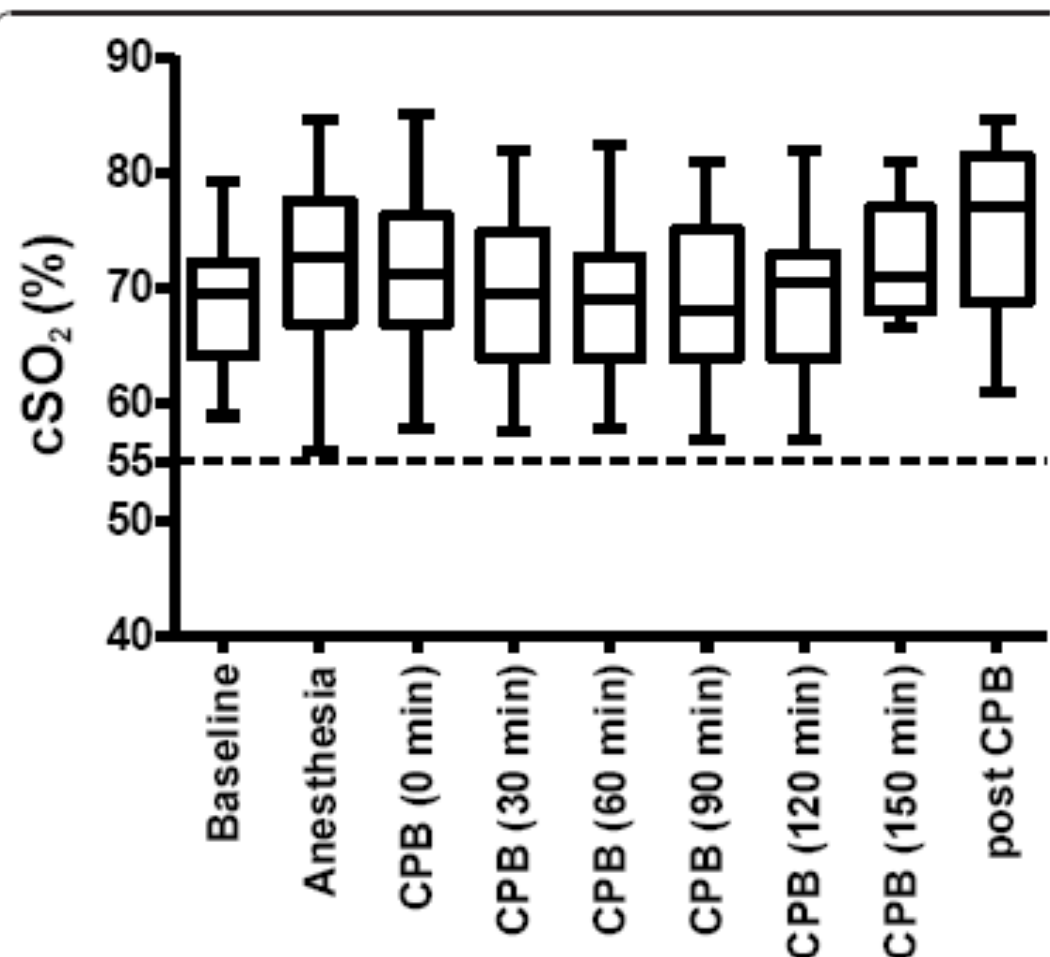


Figure 1 Cerebral oxygen saturation (cSO₂) at points of interest before induction of anaesthesia (Baseline), during anaesthesia before cardiopulmonary bypass (Anaesthesia), during cardiopulmonary bypass (CPB, 0 min - 150 min) and during anaesthesia after cardiopulmonary bypass (post CPB). The additional grid line shows the absolute lower limit of cSO₂ (55%). Data is given as median, 25th/75th percentile and range.

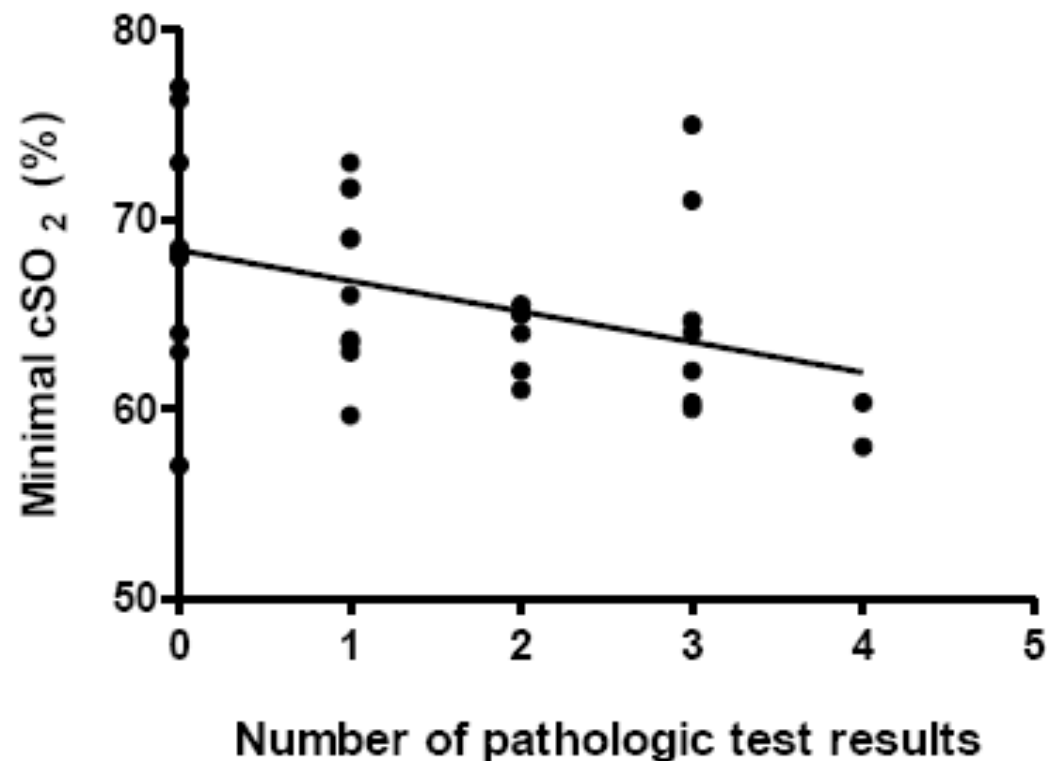


Figure 2 Correlation of severity of postoperative neurocognitive deficit (POCD) defined as the number of tests with clinically relevant decline (decrease of postoperative test results below 80% of preoperative baseline) after cardiac surgery with minimal cSO₂ during cardiopulmonary bypass by trend ($p = 0.015$, $r^2 = 0.44$, without Bonferroni correction). POCD was investigated by a set of five neuropsychological tests 1 day before and 4 days after heart surgery with cardiopulmonary bypass.

文章的结果

- **POCD的发生率为43%**
- **最低cSO₂与POCD显著相关 ($p = 0.015$, $r^2 = 0.44$)**
- **预测发生POCD的cSO₂ 阈值是65% (sensitivity : 86.7% ; specificity: 65.0%**

麻醉技术

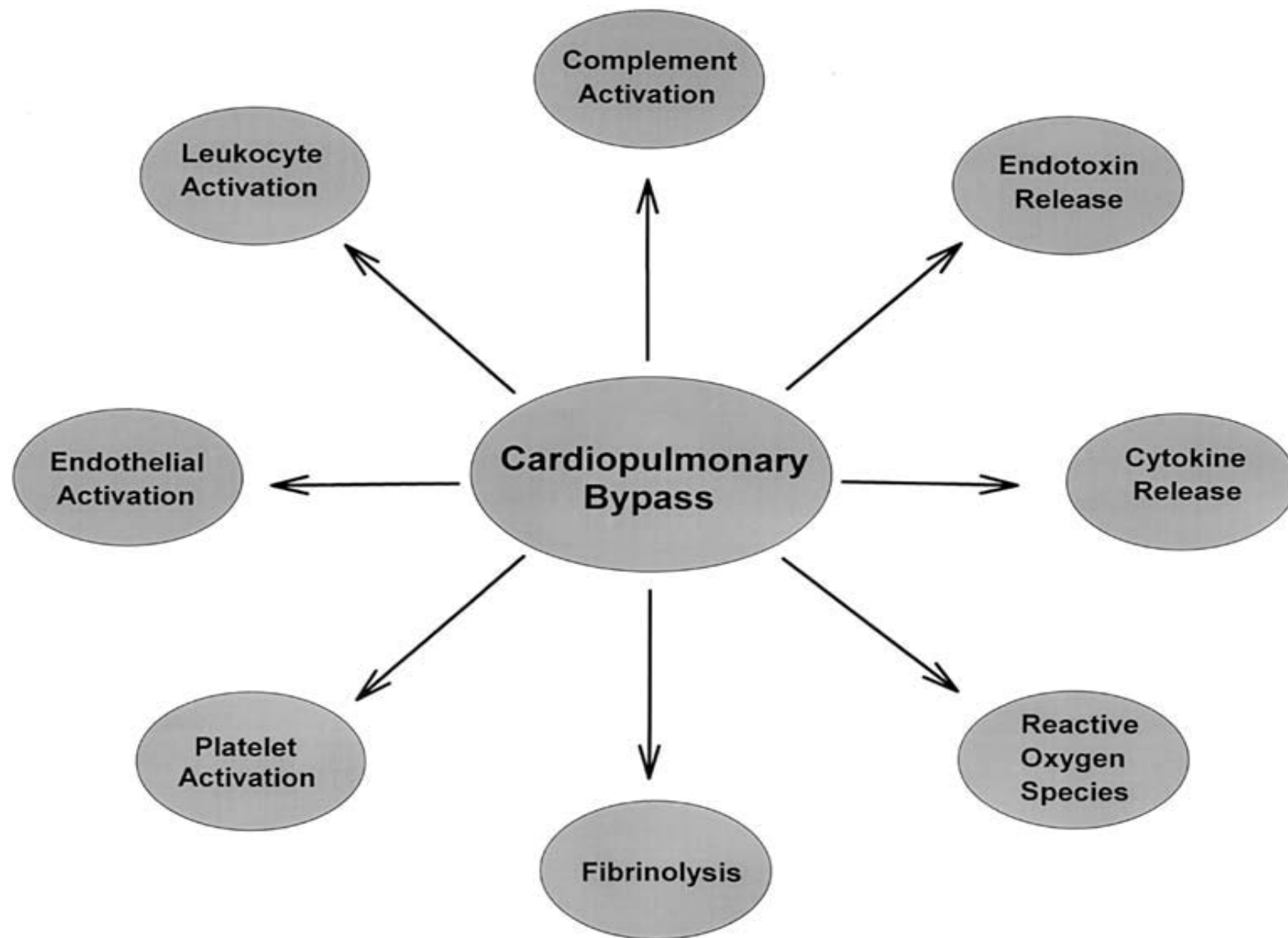
- 适当监测 TCD、EEG、TEE、 S_JO_2
- 禁用笑气
- 及时、正确处理各种生理异常
- 多种保护药物应用？

- 使用主动脉超声监测可以有效降低心脏手术后早期卒中的发生。

Zingone,B; Rauber,E; Gatti,G: The impact of epiaortic ultrasonographic scanning on the risk of perioperative stroke. Eur J Cardiothorac Surg 2006 May; 29(5): 720-8

麻醉技术

- 脑低灌注
原因：脑静脉回流不畅、低动脉压、低**PaCO₂**、心脏移位、极度转头
监测：**cerebral oximetry, TCD, EEG**
处理：对因治疗
- 炎性和代谢
高血糖：**>6.1mmol/l**，每增加**1mmol/l**，风险增加**17%**。
要严格控制血糖！
脑温、体温高
毛细血管通透性增加、白细胞聚集、补体激活、



CPB与全身炎症反应

脑保护药物

- u** 利多卡因 1.5mg/kg 4mg/kg 4mg/min
- u** 硫喷妥钠1g
- u** 甲基强的松龙 30mg/kg
- u** 苯妥英钠1g

Randomized, Double-Blinded, Placebo Controlled Study of Neuroprotection With Lidocaine in Cardiac Surgery

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Hilary P. Grocott, MD; Donald D. Glower, MD; Daniel T. Laskowitz, MD;
James A. Blumenthal, PhD; Mark F. Newman, MD;
for the Neurologic Outcome Research Group (NORG) of the Duke Heart Center*

stroke,2009;40:880-887

研究目的：考察静脉**lidocaine**对体外循环心脏术后对认知功能损害的改善作用

方法：**277**例病人，前瞻性、随即分组、双盲安慰剂对照、单中心研究。一组病人**114**例：**Lidocaine 1mg/kg, bolus iv infusion**直至术后**48h**。另一组**127**例：安慰剂生理盐水。术后**6w**、**1**年测定认知功能。

结果：两组认知功能损害发生率分别**45.5%**和**45.7%**（**P=0.97**）。**Lido**处理与糖尿病对认知损害有明显相互作用（**P=0.004**）。**Lido**剂量是认知损害的预测因子。低浓度**liduo**显示在非糖尿病病人中有保护作用。

结论：**lidocaine**对心脏术后认知功能损害高发生率无改善。大剂量**lidocaine**和糖尿病是认知损害的独立预测因子。小剂量对非糖尿病病人的保护作用需要进一步评估

Table 2. Multivariable Linear Regression Model Predicting Cognitive Change (continuous outcome) at 6-Week Follow-Up

Variable	DF	Parameter Estimate (95% confidence limits)	<i>P</i> Value
Age	1	−0.009 (−0.012 to −0.005)	<0.001
Years of education	1	0.012 (−0.002 to 0.027)	0.098
Weight	1	0.002 (−0.0001 to 0.004)	0.070
Preoperative cognitive index	1	−0.264 (−0.372 to −0.156)	<0.001
Lidocaine treatment	1	0.074 (−0.016 to 0.164)	0.108
Diabetes	1	0.031 (−0.111 to 0.172)	0.671
Diabetes · Lidocaine	1	−0.291 (−0.489 to −0.093)	0.004

*DF indicates degrees of freedom.

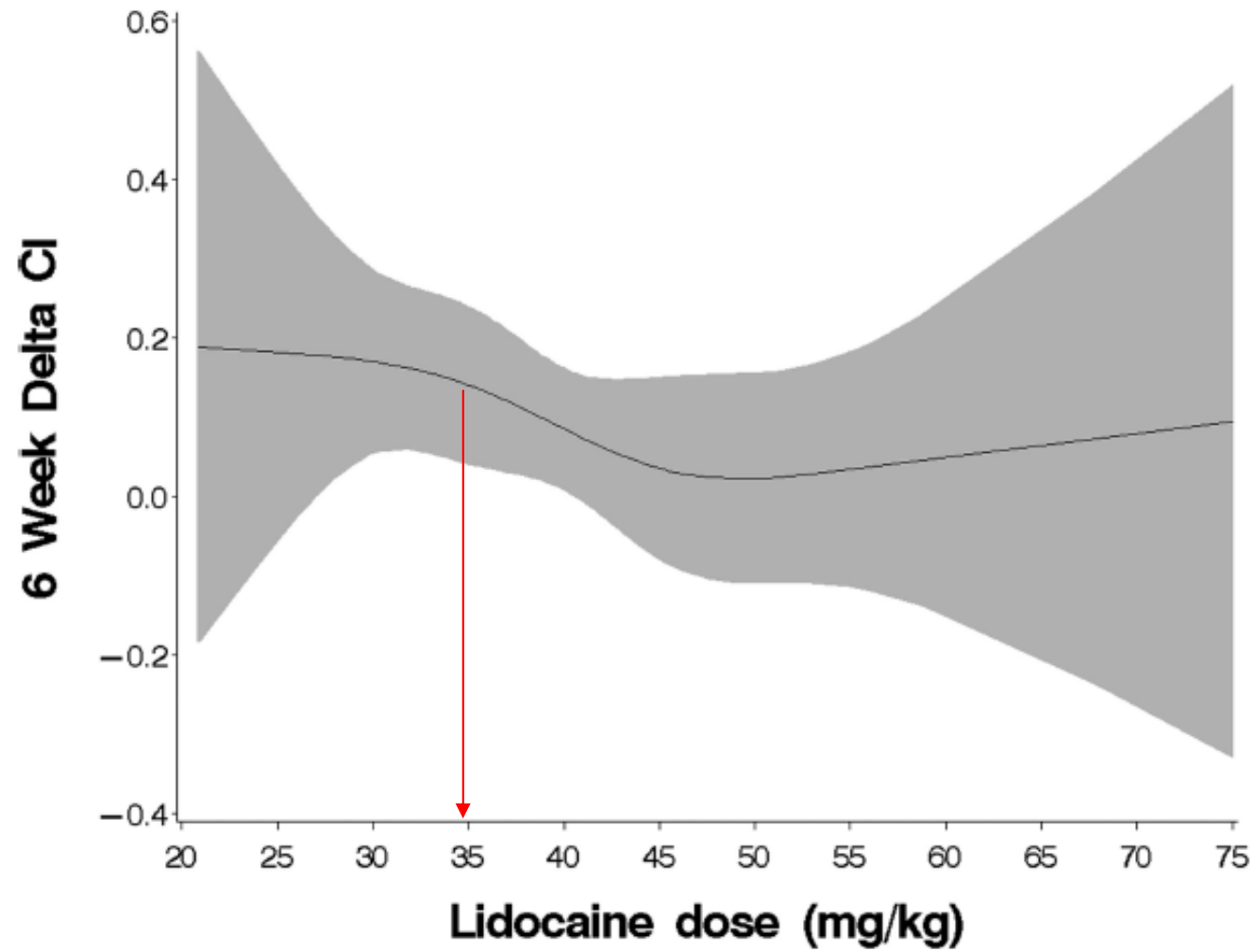
**Lidocaine与糖尿病交互作用是术后认知损害的预测因子，
P=0.004**

以下是**lidocaine**组结果，由于剂量不是按体重给与，因此体重越轻的病人剂量越大。显示**lidocaine**剂量大是认知功能损害的预测因素（独立于糖尿病因素）， **P=0.029**

Table 3. Multivariable Linear Regression Model Predicting Cognitive Change (continuous outcome) at 6-Week Follow-Up in the Lidocaine Group Only

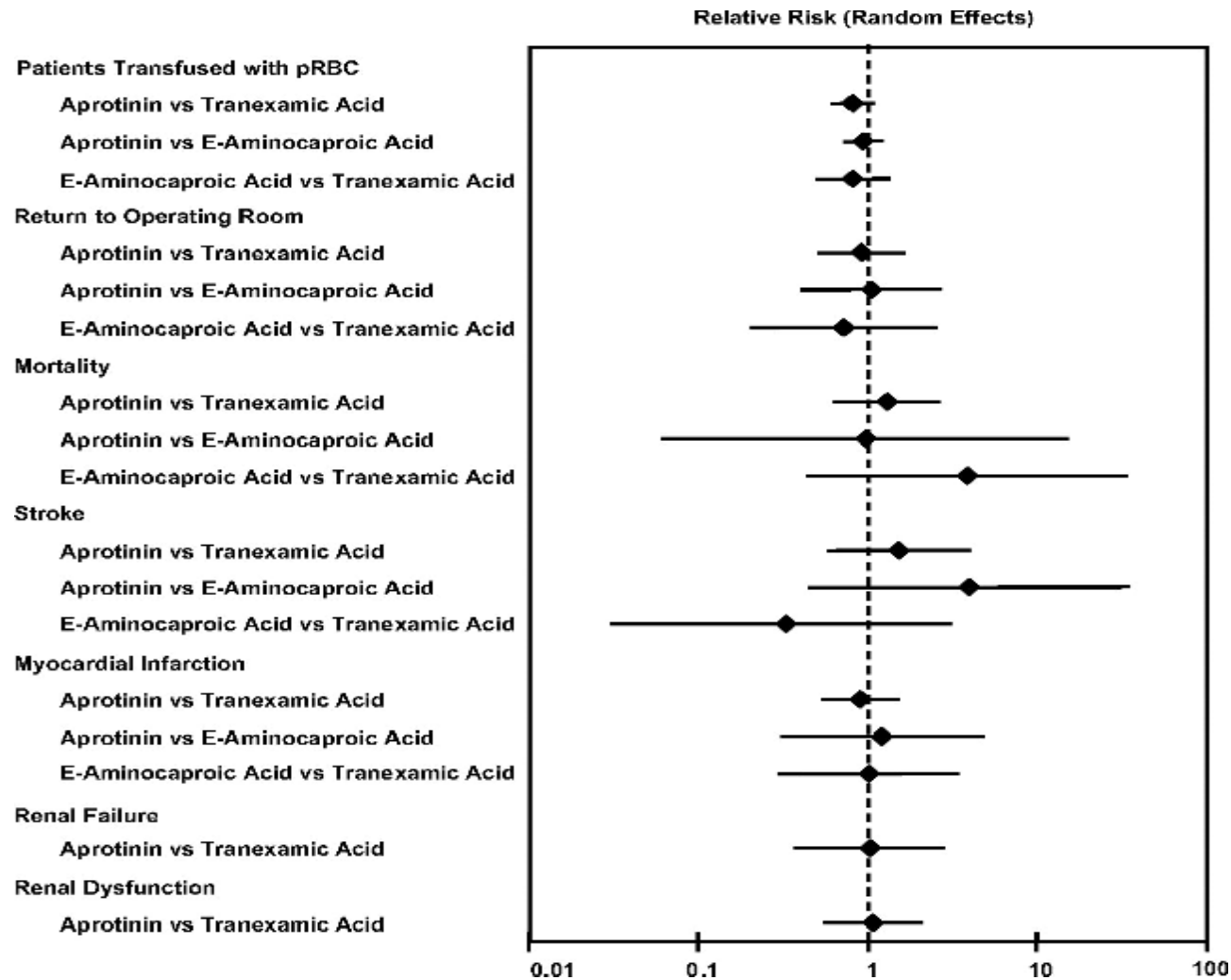
Variable	DF	Parameter Estimate (95% confidence limits)	P Value
Age	1	−0.006 (−0.011 to −0.008)	0.024
Preoperative cognitive index	1	−0.208 (−0.336 to −0.079)	0.002
Diabetes	1	−0.283 (−0.425 to −0.142)	<0.001
Lidocaine dose, mg/kg	1	−0.008 (−0.015 to −0.001)	0.029

*DF indicates degrees of freedom.



随lidocaine剂量增加，认知功能降低，阈值可能在35mg/kg

抗纤维蛋白溶解药物的副作用比较: head-to-head comparison



位于1.0左侧表明对前者药物有利

位于1.0右侧表明对后者药物有利

Steroid

- 减轻炎性反应，对预防卒中有效吗？
- **NO!**

	Steroid	Control
人数：	98	98
观察：	死亡率、卒中、肾衰、腹部并发症、伤口感染等	
结果：	两组无差别，但伤口愈合和机械通气 S 组时间长	

Pai,KR; Ramnarine,IR; Grayson,AD: The effect of chronic steroid therapy on outcomes following cardiac surgery: a propensity-matched analysis. Eur J Cardiothorac Surg. 2005 Jul; 28(1): 138-42

MgSO₄有效？

- 性质：随机、盲法、对照研究
- 分组：硫酸镁组 无干预对照组
- 人数：174 176
- CPB中使硫酸镁的血浓度为正常的2倍
- 观察：术前、拔管24h、96h的神经功能（短期记忆、出现原始反射）、术后3m的精神及抑郁情况
- 结果：卒中人数2: 5, $P=0.4$;
- 神经功能评分较好, $P<0.0001$
- 3m的精神和抑郁无差异
- 结论：硫酸镁近期有脑保护作用，但还需进一步研究

Bhudia,SK; Cosgrove,DM; Naugle,RI: Magnesium as a neuroprotectant in cardiac surgery: a randomized clinical trial. J Thorac Cardiovasc Surg 2006 Apr; 131(4): 853-61

Statins(沙丁类)

回顾研究，术前服用，观察至术后30d

	Statin	降脂药	P
人数	943	720	
术后卒中	4.6%	7.1%	<0.05

Pan,W; Pinter,T; Anton,J: Statins are associated with a reduced incidence of perioperative mortality after coronary artery bypass graft surgery. Circulation. 2004 Sep 14; 110(11 Suppl 1): II45-9

沙丁长期服药研究证明：降低卒中率，且改善预后

- 降血脂
- 改善内皮功能
- 增加**NO**的生物利用度，上调**NO**合成酶活性
- 抗氧化
- 抑制炎症反应
- 免疫调节
- 稳定硬化斑块

问题

- 沙丁能否在卒中发生后给药而改善预后？

注意！

- 突然停药会使心脑血管不良事件增加

Mathias Endres: Statins and stroke. J Cereb Blood Flow Metab 2005;25,1093-1110

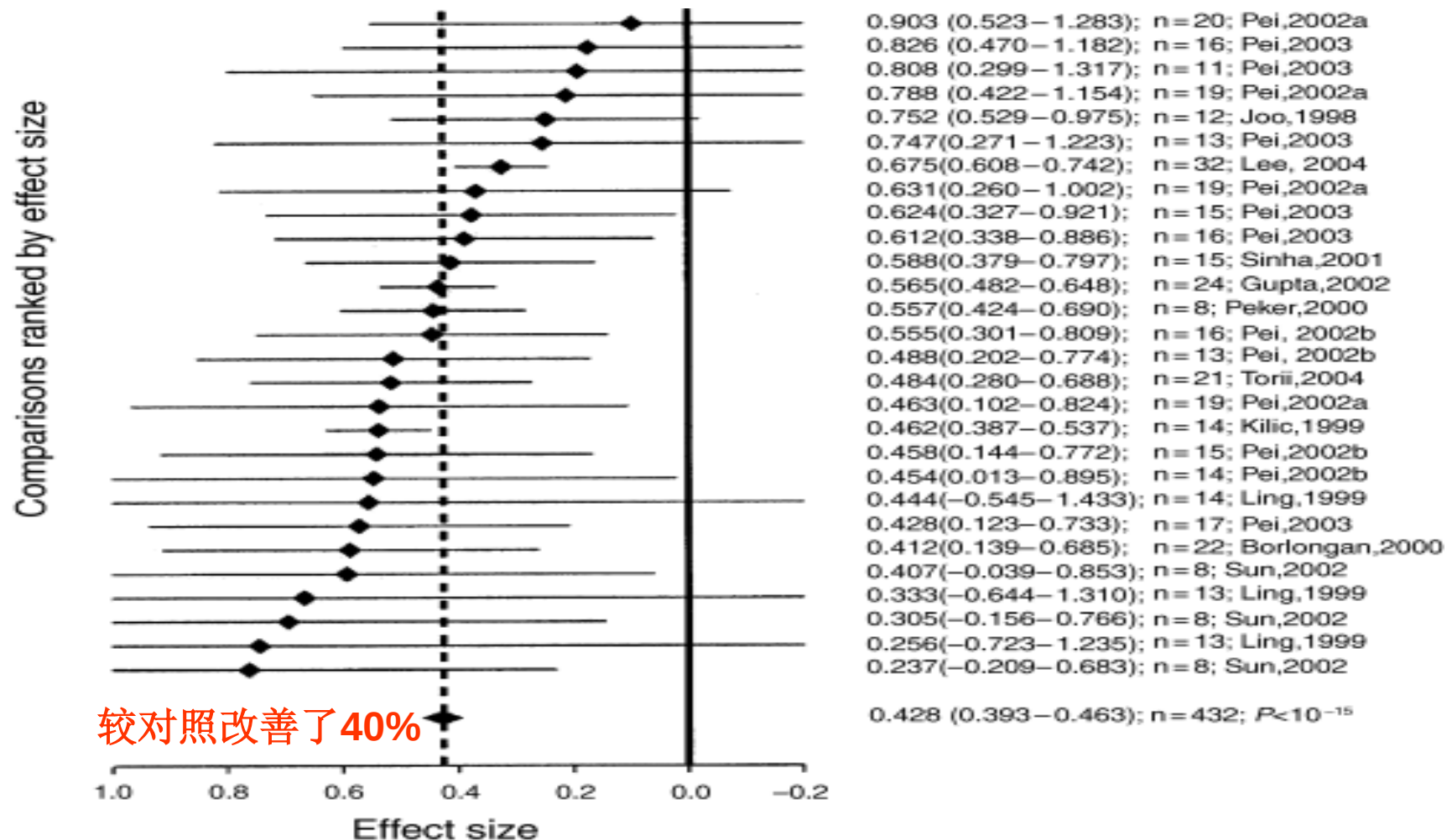
Melatonin

- 动物试验有效（局灶、全脑缺血性脑梗塞）
- 人？（待研究）

Melatonin动物试验结果荟萃分析

Malcolm R. Macleod, Tori O'Collins, Systematic review and meta-analysis of the efficacy of melatonin in experimental stroke. Journal of Pineal Research 38 (1), 35-41, 2005

对照= Mltnn.



补体激活抑制药物

pexelizumab（人C5单克隆抗体）

- 前瞻、随机、双盲、对照、II期临床
- **914病人**
- 观察：术后**4d**、**30d**认知功能等
- 结果：仅对视觉空间有改善（**P=0.003**）

Mathew,JP; Shernan,SK; White,WD: Preliminary report of the effects of complement suppression with pexelizumab on neurocognitive decline after coronary artery bypass graft surgery.Stroke 2004 Oct; 35(10): 2335-9

成人心脏手术时药物神经保护的随机对照研究

Table 4. Randomized, Placebo-Controlled, Trials of Pharmacologic Neuroprotection for Adults Undergoing Cardiac Surgery

Drug	Proposed primary mechanism	Author	n	Type of surgery	Main findings
Thiopental	↓ CMRO ₂	Nussmeier et al (222)	182	Valvular	Thiopental ↓ cognitive complications 10 days after surgery.
		Zaidan et al (223)	300	CABG	No difference in neurologic outcomes thiopental versus placebo.
Propofol	↓ CMRO ₂	Roach et al (224)	225	Valvular	No difference in cognitive complications 5–7 days or 50–70 days after surgery propofol versus controls.
Nimodipine	Ca ⁺⁺ channel blocker	Legault et al (225)	150	Valvular	Study terminated early due to higher mortality in treated versus control group; no evidence of benefit with nimodipine on cognitive outcomes.
Prostacyclin	↓ platelet aggregation, ↓ inflammation	Fish et al (226)	100	CABG	No difference in cognitive outcomes 2 wk after surgery between treated and control patients.
GM1 ganglioside	↓ EAA signaling	Grieco et al (227)	29	CABG ± valvular	Pilot study finding no difference cognitive outcomes between treated and control patients.
Remacemide	NMDA receptor antagonist	Arrowsmith et al (228)	171	CABG	Remacemide led to better performance on 3 of 10 psychometric measures and better global cognitive function.
Pegorgotein	Antioxidant	Butterworth et al (229)	67	CABG	Study stopped before completion; no drug benefit in reducing the rate of neurocognitive dysfunction.
Aprotinin	Mechanism(s) unknown; maybe due to ↓ inflammation/ ↓ pericardial aspirate	Levy et al (230)	287	CABG	No strokes in “high” and “low” dose aprotinin groups versus controls (n = 5) and “pump” prime only (n = 1) groups (P = 0.01).
		Harmon et al (231)	36	CABG	Cognitive deficits 6 weeks after surgery lower in aprotinin versus placebo group (23% versus 55%, P < 0.05).
Lidocaine	Na ⁺ channel blockade; membrane stabilization/ ↓ EAA release	Mitchell et al (232)	55	Valvular	Neurocognitive outcome better 10 days and 10 wk after surgery in lidocaine versus placebo group but not at 6 mo.
		Wang et al (233)	42	CABG	Improved neurocognitive function 9 days after surgery with lidocaine versus placebo.
Clomethiazole	GABA receptor agonist	Kong et al (234)	219	CABG	No difference in neurocognitive function 4–7 wk after surgery in clomethiazole versus placebo groups.
Pexelizumab	↓ C5a and C5b-9	Mathew (235)	800	CABG	Pexelizumab had no effect on global cognition but did lower decline in the visuo-spatial domain compared with placebo.

CMRO₂ = cerebral metabolic rate for oxygen; CABG = coronary artery bypass grafts; EAA = excitatory amino acid; NMDA = N-methyl-D-aspartate; GABA = gamma-aminobutyric acid.

ACC/AHA推荐

分级

证据水平

Class I 治疗有效（证据、意见一致）

Level A: 多中心、随机临床试验

Class II 应该采用

B: 单中心随机或非随机试验

Class II A 需要目的明确的更多研究

C: 专家一致意见

Class II B 需要目的广泛的更多研究；更多的登记数据也有帮助

Class III 不该采用、无效或有害

Evidence-based 指南

- 1, 成人应用中度低温CPB, pH应采用a-stat管理 (class I, level A)
- 2, 控制动脉管路于37℃对避免脑部高温可能有利 (class II A, level B)
- 3, 应将所有病人的血糖控制在正常, 包括非糖尿病人 (class I, level B)
- 4, 避免直接回输心腔切开和纵膈回收血 (class I, level B)
回收血的输入应进行处理和过滤, 可减少不良反应 (class II B, level B)
- 5, 有高危卒中因素的病人, 强力推荐使用TEE或主动脉超声检查, 以便:
检查不可摸到的斑块 (class I, level A)
减少脑栓塞 (class II A, level B)
- 6, 应在动脉管路加装滤器以减少栓子量 (class I, level A)
- 7, 应努力减少血液稀释 (Hct>27%), 包括减少预充液以减少异体输血 (class I, level A)
- 8, 减少管道的接触面积和使用组织相容性好的生物材料以减少CPB炎性反应, 可改善预后 (class II A, level B)

Kenneth G Shann et al: An evidence-based review of the practice of cardiopulmonary bypass in adults: A focus on neurologic injury, glycemic control, hemodilution, and the inflammatory response. J Thorac Cardiovas Surg 2006;132(2):283-90

Evidence-Based Ratings for Pharmacologic and Nonpharmacologic Neuroprotection during Cardiopulmonary Bypass

Table 6. Evidence-Based Ratings for Pharmacologic and Nonpharmacologic Neuroprotection during Cardiopulmonary Bypass (see Text and Table 5 for Criteria)

Intervention	Rating
Heparin-bonded CPB circuits	Class Indeterminate
Epiaortic ultrasound-guided changes in surgical approach	Class IIb
Modified aortic cannula	Class Indeterminate
Leukocyte-depleting filters	Class Indeterminate
Cell-saver processing of pericardial aspirate	Class Indeterminate
CO ₂ wound insufflation	Class Indeterminate
Maintaining "higher" MAP targets (i.e., > than lower target of 50 mm Hg)	Class IIb for patients at high risk for neurologic injury
Non-pulsatile (versus pulsatile) perfusion	Class IIb (Class Indeterminate for patients at high risk for neurologic injury)
α -stat (versus pH-stat) acid base management	Class IIb (Class Indeterminate for patients at high risk for neurologic injury)
Minimal hematocrit target during CPB of >27%*	Class Indeterminate
Thiopental, propofol, nimodipine, prostacylin, GM1 ganglioside, pegorgotein, clomethiazole	Class III
Remacemide, lidocaine, aprotinin, pexelizumab	Class Indeterminate
"Tight" glucose intraoperative control	Class Indeterminate
Hypothermia	Class Indeterminate

*The optimal hematocrit during CPB is not defined by available data. A hematocrit of >27% chosen as indicative of "high" hematocrit based on its use in available randomized trials (see text).
CPB = cardiopulmonary bypass; MAP = mean arterial blood pressure.

CPB管路肝素化

能减轻炎症反应
是否影响预后？

Heparin-bonded circuits versus
nonheparin-bonded circuits:an evaluation
of their effect on clinical outcomes

*European Journal of Cardio-
thoracic Surgery*31(2007)1058—
1069

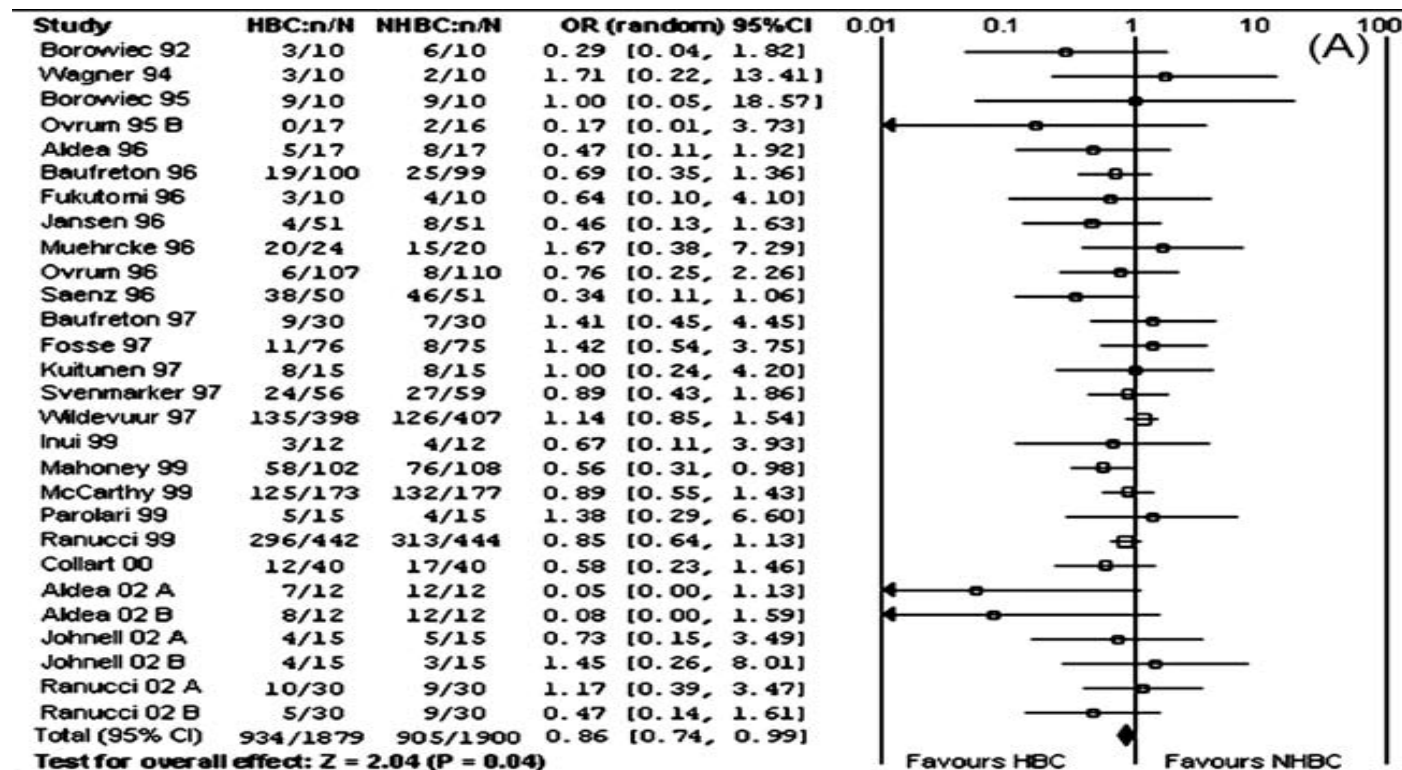
文献荟萃分析

41个随机研究，3434个病人进入分析

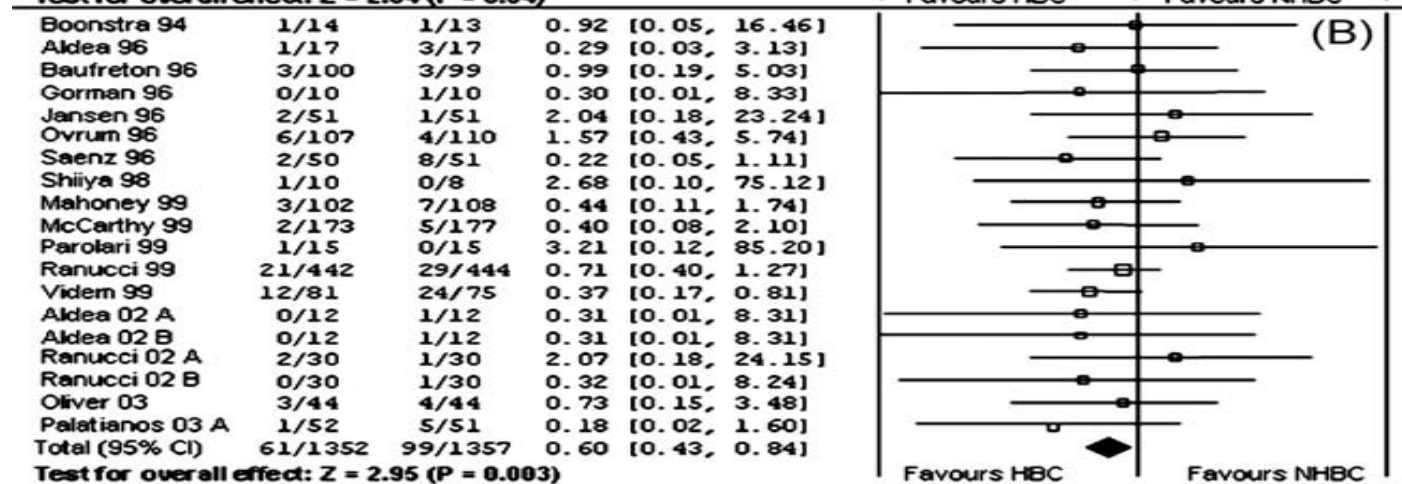
是否HBCs在死亡率、病残率等方面优于non-HBCs

- ü 输血及血液制品
- ü 死亡率
- ü 急性心梗
- ü 脑卒中
- ü 再次开胸
- ü 伤口感染
- ü 房颤
- ü 机械通气时间
- ü ICU滞留期
- ü 住院日

(A) 术后24h失血量



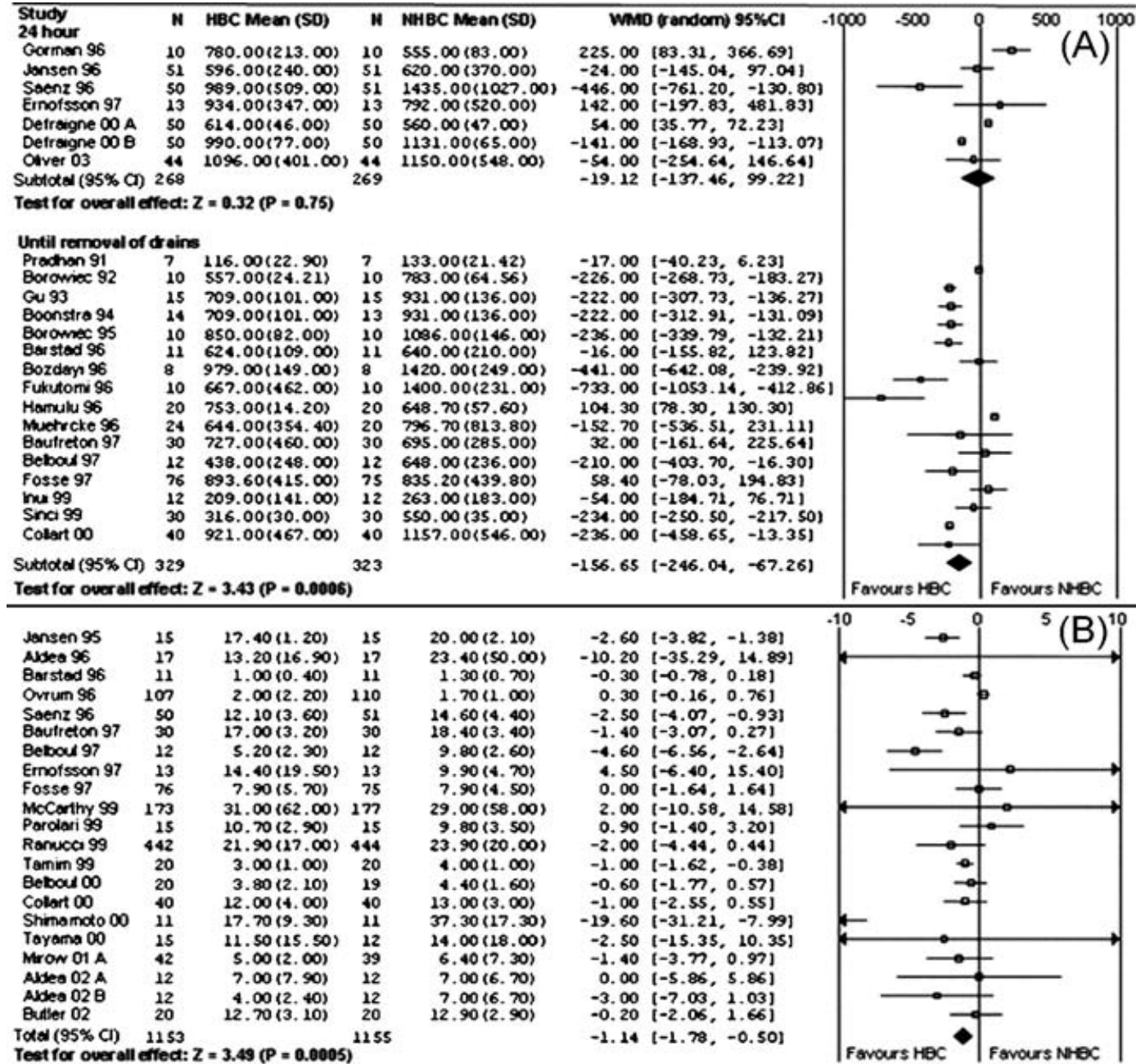
(B) 术后24h输血率



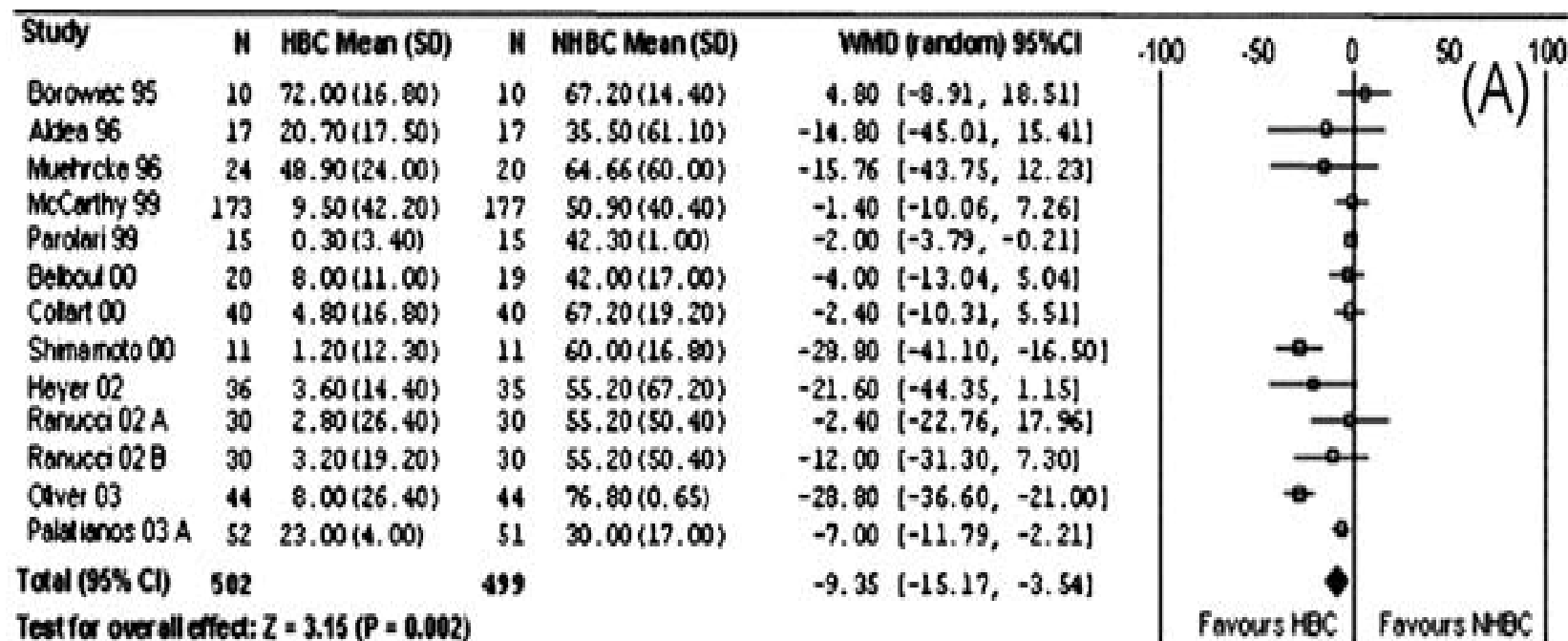
(A)
通气时间

(C)
住院时间

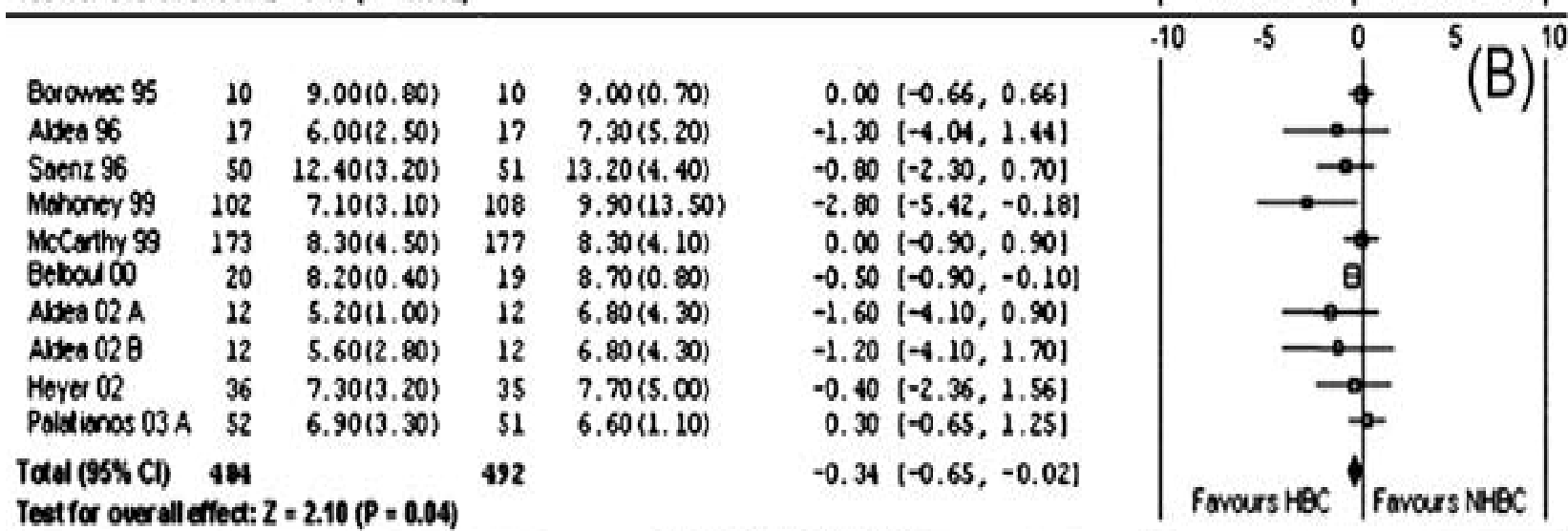
(B)
ICU
滞留时间



(A)
再次开胸



(B)
死亡、心梗、卒中、伤口感染等



结论

肝素化管路对病人预后有利

严重脑缺血的治疗原则

轻度高血压

MAP 80-90mmHg

中度过度通气

PaCO₂ 25-35mmHg

中度高氧血症

PaO₂>100mmHg

pH、电解质、渗透压、血糖、血球压积、体温

正常

镇静、制动、抗惊厥

渗透性利尿

皮质激素

氢化可的松 300mg/d

地塞米松 0.2mg/Kg 6日

液体和营养

30ml/Kg.d

50Kcal/Kg.d

谢谢光临

