## Introduction: Outcomes 2006

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This year was the 10th anniversary of Outcomes, which was again held at the Casa Marina Resort in Key West, Florida, May 17 through May 20, 2006. There were more than 190 registrants from research and clinical sites throughout North America, as well as Italy, Germany, U.K., France, New Zealand, Australia, and other international locales. The multidisciplinary nature of this meeting is recognized for providing an expert forum in which to discuss issues related to brain protection for patients undergoing a variety of cardiac and other surgical procedures. Registrants included cardiac and vascular surgeons, anesthesiologists, perfusionists, neurologists, neuropsychologists, cardiologists, nurses, and psychometrists, as well as industry representatives. Given this mix of expert clinicians and scientists, as well as the high levels of attendance from researchers, technicians, and industry representatives, the interest level at the various lectures, discussions and question and answer sessions was very strong.

A remarkably consistent feature of the meeting is the number of new scientific paper presentations that directly address issues and concepts initially raised in discussion at the Outcomes meeting of the previous year. One highlight of this year's meeting was the summary presentation of the "Best Practices CPB" guidelines which have now been published (J Thorac Cardiovasc Surg 2006:132;283-90). This publication represents a significant accomplishment for this multidisciplinary group, which comprises perfusionists, anesthesiologists, cardiac surgeons, and epidemiologists. A number of evidence-based topics-many of which had initially been presented at previous Outcomes meetings-were critically evaluated and rated, with management recommendations made. Use of epi-aortic scanning, alpha-stat pH management, tight glucose control, use of arterial line filtration, avoidance of retransfusion of unprocessed shed blood, avoidance of hyperthermia by limiting arterial blood inflow temperature to 37°C, minimization of dilutional anemia, and steps to minimize inflammatory response have all been highlighted in previous Outcomes meetings, in many cases reflecting original research initially presented at Outcomes over the past decade. As organizers, we are very gratified by this. It clearly demonstrates the value of the premise that underlies the format of the Outcomes meetings, emphasizing discussion and interaction amongst researchers and clinicians.

For next year's meeting, the venue will be changed. After discussion with many of the registrants we felt it was a time for renewal, so "Outcomes XI, 2007" will be held at Accra Beach Hotel and Resort in Barbados, W.I., May 9-12, 2007. This is an excellent hotel that offers both a relaxed oceanfront setting with private beach and optimal conference space and meeting facilities. A reminder notice is posted at the end of these Proceedings and further information can be found at our website: www.outcomeskeywest.com. We will strive to maintain the same ideal mix of state-of-the-art lectures and scientific abstracts with a heavy emphasis on Q&A and audience interaction and discussion. Next year one particular focus will be on the role of inflammatory processes and mechanisms-so you can plan your abstract submission accordingly, although there is always opportunity for abstracts dealing with the myriad of other issues of concern.

Last, we would like to acknowledge the efforts of all those individuals without whose assistance none of this would have been possible. The support of our sponsors as well as the efforts of our own staff from both Wake Forest University and University Hospital-London Health Sciences Centre was outstanding. Special thanks to Dwight Deal, Paige Deal, and Peggy Rachels, and Sandy Adams, Steven Dain, Catherine Hawke, Colin Murkin, and Marigo Portokalis. Ultimately, thanks for the overall success of this Outcomes meeting, as well as for the high quality of the scientific papers as published in these Proceedings, must go to all those participants, registrants, lecturers, and staff who contributed so much to the success of this year's program. Thanks to you all. We hope to see you next year at "Outcomes XI, 2007," May 9-12, 2007. Please note in order to facilitate planning and minimize registration lines, etc., all abstract submission and meeting registration for Outcomes 2007 must be done via the website. For further information, registration, and abstract submission details visit our website at www.outcomeskeywest.com.

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Edwards Lifesciences

# Statistical Interpretation: The Art and Occasional Science

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## INTRODUCTION

Statistics are a vehicle to confirm or refute, using lawful, repeatable, mathematical manipulations, what you can generally see with your eyes or via clinical intuition. However, if the wrong question is asked or an inappropriate statistical or experimental design is employed, an erroneous conclusion can be foisted upon an unsophisticated audience. Furthermore, if insufficient information concerning the statistical analysis is provided in a published paper then it is difficult to interpret the results. Perhaps as a consequence, many studies are contradicted within a short period of time, leading the public to develop skepticism that, once present, is hard to reverse; these quotes from the recent *New York Times* article "For Science's Gatekeepers, a Credibility Gap" [Altman 2006] underscore this process:

Recent disclosures of fraudulent or flawed studies in medical and scientific journals have called into question as never before the merits of their peer-review system ...

... Virtually every major scientific and medical journal has been humbled recently by publishing findings that are later discredited.

The field of applied statistics has grown immensely during the past 20 years. Innovations in mathematical formulations as well as the increased availability of complex computerbased algorithms have led to methodological advances in nearly all fields of science [Raftery 2001]. This growth has been instrumental in the advancement of knowledge, but because medical education has not similarly evolved in respect to the teaching of modern statistical methods this growth has also served to distance the physician-scientist from several aspects of the scientific endeavor. Because of the increasing

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Address correspondence and reprint requests to: David A. Stump, PhD, Department of Anesthesiology, Wake Forest University School of Medicine, Winston-Salem, NC 27157-1009, USA; 1-336-716-7194; fax: 1-336-716-3909 (e-mail: dstump@wfubmc.edu). use of novel statistics in basic medical research, our physician colleagues are at times left to wonder: "What do these results really mean?"

To help us illustrate these points, Dr. Robert Poston kindly allowed us to examine the data from his study, which recently examined the use of aprotinin during off-pump coronary artery bypass grafting [Poston 2006]. Several endpoints were examined including blood loss, platelet function, and thrombotic events. As part of a secondary analysis, the authors utilized parametric statistical methods to examine the total costs associated with the use of aprotinin compared to those of a placebo. Although not directly examined by the authors, a subset of the total costs, the operating room (OR) cost, was available and is the subject of this analysis.

The present analysis illustrates the examination of several assumptions underlying a parametric statistical approach. The consequences of omitting relevant sample statistics (mean, standard deviation, etc) used to evaluate such an approach are demonstrated through several statistical tests conducted with very different results.

## METHOD

## Subjects and Procedure

Sixty patients were randomly assigned to receive either aprotinin (n = 29) or a placebo (n = 31) during their surgery. For more information on subjects and data collection methods, see Poston et al [2006].

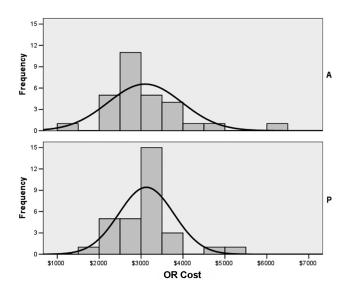
## **Statistical Analyses**

The present analysis examines the OR costs associated with the aprotinin and placebo conditions. In so doing, several commonly used descriptive statistics are reported.

*Mean.* The average cost (the total cost for each patient divided by the number of patients). This is the measure of central tendency that is most commonly used and is the one used in conducting t tests.

*Median*. The midpoint, half the costs are above, half below. The median of a group of numbers is a more accurate representation of their center when they are skewed (see below).

*Mode.* The most frequent cost. The modal value is the one most frequently observed in a set of numbers.



The distribution of operating room (OR) cost is presented for each group. A indicates aprotinin group; P, placebo group.

*Standard deviation*. A measure of spread around the mean. *Skewness*. The lack of symmetry around the mean. Outlying values can cause distributions to be more skewed than would be expected given a normal distribution.

*Kurtosis.* A measure of the concentration of scores around the mean. Scores can be more (leptokurtotic) or less (platokurtotic) bunched around the mean than would be expected given a normal distribution.

A histogram, which is a common graphical technique, is used to better examine the distributions of the data. An independent samples *t* test is used for pedagogical reasons to evaluate differences between groups. For this comparison, the experimental hypothesis (H<sub>1</sub>) is that the OR costs incurred by patients who take aprotinin are different than the costs incurred by patients who take a placebo (with the null hypothesis [H<sub>0</sub>] being that the conditions do not differ). This nondirectional hypothesis implies a 2-tailed test of significance that will be interpreted at the  $\alpha = .05$  level. Finally, a logistic regression is used, again for pedagogical purposes, to index the location of scores above and below the median.

## Statistical Assumptions

The vast majority of conducted statistics in medicine are referred to as parametric statistics (eg, t tests and analysis of variance). For parametric tests to produce accurate results, the data being analyzed must be compared to one of a known family of probability distributions (ie, the probability that these groups differ by chance factors alone). It is precisely for this reason that these tests require that the data meet certain key assumptions, 2 of which, a normal distribution and homogeneity of variances, are often violated by clinical data. A normal (Gaussian) distribution is quite familiar to most researchers, but even this key concept is worth examining in further detail and must be examined prior to the initiation of any inferential procedure utilizing parametric statistics.

A second key assumption is homogeneity of variance (and covariance). This assumption mandates that the variances of groups that are being compared must be sufficiently similar for the comparison to be meaningful. Too often analysts fail to consider this assumption and base their conclusions on a dubious statistical result. In what follows, an example of the OR costs incurred by a group of cardiac patients treated with aprotinin or a placebo is presented to illustrate the problems of outlying observations and their effect on the homogeneity of variances assumption.

## Statistical Power

Prior to undertaking the analysis, or better yet, conducting the study, it is wise to examine the size of the differences that are able to be detected with the available (or proposed) sample size. In essence, statistical power is the probability that statistically significant results will be obtained (for a more advanced understanding, see Cohen [1988]). For the present example using a *t* test, with a group size of roughly n = 30(N = 60), and a 2-tailed significance test at  $\alpha = .05$ , there is an 80% chance that statistical significance will be obtained when the group means differ by .74 standard deviation units (d = .74) [Cohen 1988]. Thus, for statistical significance to be obtained in the current analysis, the observed effect will have to be quite large, with approximately 44% of the aprotinin group's OR costs not overlapping the placebo group's costs (and occurring in the same direction, either higher or lower).

## RESULTS

The distribution of OR cost is presented for each group in the Figure with corresponding descriptive statistics presented in the Table. Both the Table and an "ocular" analysis of the Figure indicate that the aprotinin group's OR costs are on average less (on all 3 measures of central tendency: mean, median, mode) but are more variable, having a larger standard deviation.

The aprotinin and placebo groups are roughly distributed normally, but are more positively skewed (1.7 and 1.1, respectively) and taller (leptokurtic: 5.7 and 3.0, respectively) than would be expected with a normal distribution (Figure). In the case of the aprotinin group, the skew appears to be due in large part to an outlying patient whose costs are considerably

Descriptive Statistics of Operating Room Cost

	Aprotinin	Placebo
Mean	\$3094	\$3125
Median	\$2954	\$3147
Mode	\$1303	\$2496
Standard deviation	\$882	\$657
Skewness	1.7 (.43)	1.1 (.42)
Kurtosis	5.7 (.85)	3.0 (.82)

higher than the next-highest patient cost. It is very difficult to formally assess the normality of small samples (like in the present example), but parametric tests are generally robust to small violations of normality.

A formal test of the homogeneity of variances assumption, Levene's test, failed to reject the null hypothesis that the 2 groups have equivalent variances, F (1, 58) = .76, P = .39. Thus, for the present example, the 2 variances will be viewed as being equivalent.

A *t* test failed to reject the null hypothesis that the groups differed in cost, t (58) = .15, P = .88. After considering the power calculations and the way a *t* test is calculated, this result is intuitive. For instance, the means of the 2 groups are very similar, and the variability within groups is quite large, resulting in a very small effect size, d = .04. The interpretation of this test result could be that the use of aprotinin is equivalent to the use of a placebo for OR costs.

However, further inspection of the Figure may lead to a different conclusion. If there are no differences between the groups (ie, the average costs are the same), then it is reasonable to assume that an equal number of patients in the aprotinin group should fall below the median (of all of the patients) as above. However, for the present data this is not the case, with aprotinin patients being 3.1 times more likely than placebo patients to incur less than the median cost: odds ratio, 3.1 (95% CI, 1.06-8.90); P = .038. This effect can be seen in the Figure, as the modal OR cost for aprotinin is \$1193 less than for the placebo.

## DISCUSSION

The present analysis demonstrates the importance of reporting (and reviewing) more information than simply the mean of 2 distributions, and certainly more than a mere P value resulting from an applied statistical test. Although the results of a t test would have supported the conclusion that there were no differences in OR costs, examination of the 2 groups' medians and modes reveals that there may in fact be lower costs associated with the use of aprotinin for the typical patient (perhaps the variance in costs induced by aprotinin is greater as well, but this could not be properly evaluated in a sample this small). It turned out that a disproportionate number of aprotinin

subjects fell below the median for the combined groups, which made the median hospital cost for the aprotinin group significantly lower.

This example of the OR costs incurred by a group of cardiac patients treated with aprotinin versus a placebo illustrates the problem of outlying observations and other distributional abnormalities. The 2 groups exhibited distributions that were both positively skewed and exhibited bunching around the center. The standard deviations of the 2 groups varied considerably, but not so much that the differences were found to be significant. If the medians and modes were not included in the results section, the mismatch between these measures would have been missed; the discrepancy between them raised a red flag, indicating that the results were potentially skewed by the presence of an outlier.

These types of data are important for a hospital administrator in the current tight-budget environment. Perhaps it is more important to know what the cost is to the typical patient (modal cost \$1200 less with aprotinin) than what the average cost is for the sample. For if the costs are skewed by a few unique outliers in the study sample, the outliers cannot be counted on to appear in the next sample, emphasizing that modal cost may be a better reflection of actual cost for a specific intervention.

Perhaps now, more than ever, an understanding of basic principles of inferential statistics is crucial for the interpretation of research. In particular, knowledge of the assumptions behind parametric statistics and how these assumptions, when satisfied, might look in a graphical format (histogram) are crucial for the building of cumulative knowledge.

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## **Outcomes 2006 Abstracts**

# PERCUTANEOUS LEFT VENTRICULAR ASSIST DEVICE AS AN ADJUNCT TO OPEN HEART SURGERY

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Introduction. Percutaneous Transseptal Left Ventricular Assist Device (PTVA) has been utilized primarily to support high-risk percutaneous coronary interventions (PCI). This technology,  ${\tt TandemHeart}_{(r)}$  by Cardiac Assist, Inc., was recently employed in support of two high-risk open heart surgeries. Case Reviews. First case was a 71 year-old man who sustained a left main coronary artery dissection during elective PCI. The hemodynamics immediately deteriorated and he underwent emergent/salvage coronary artery bypass grafting times three. He was weaned off cardiopulmonary bypass (CPB) on multiple inotropes. Ten hours postoperatively, he developed progressive cardiogenic shock. The patient was taken to the cath lab where the coronary angiogram revealed all bypassed vessels to be widely patent. The PTVA system was placed by inserting a 21 French catheter into the right femoral vein, which was advanced across the atrial septum into the left atrium and a 17 French catheter into the right femoral artery. Flows were maintained at 2.5-3.0 liters/minute. His condition immediately improved. The left ventricle was supported for five days, at which time it was separated from the device at bedside. He was dismissed home five days later.

Second case involved a 52 year-old man with severe aortic stenosis and critical stenosis of the left anterior descending and right coronary arteries. The ejection fraction was 8 % and pulmonary artery pressures were 80 % of systemic. The PTVA system was placed preoperatively by inserting a 21 French cannula into the right femoral vein, advancing through the atrial septum and into the left atrium, and a 15 French cannula into the left femoral artery. Flows were maintained at 3.0-3.5 liters/minute. This was followed by aortic valve replacement and coronary artery bypass grafting times two. He was successfully weaned from CPB on minimal inotropes. The PTVA sytem was removed 12 hours later. He was dismissed to home on post-operative day 5. **Conclusion.** The PTVA sytem is an invaluable adjunct to high risk open heart surgery. Its utility was demonstrated both in prophylactic support of the high risk patient as well as in salvage of the post-cardiotomy patient with left ventricular failure.

# INITIAL US EXPERIENCE WITH THE CARDICA C-PORT DISTAL CORONARY ANASTOMOTIC DEVICE

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Introduction. In Coronary bypass surgery hand sewn distal anastomosis is the gold standard. The recent introduction of less invasive surgical techniques such as Opcab and Robotic surgery has triggered interest in the development of distal anastomotic devices to further enhance minimally invasive cardiac surgery. The Cardica C-Port device has been shown to demonstrate a 92.1% patency rate on 6-month angiography in a European study. With recently gained FDA approval this device has been deployed 160 times to date in the US. This study reports on our early experience with this device having used it to construct 76 distal anastomoses in 51 patients.

Methods. From Dec 2005 to April 2006 51 patients with either isolated coronary artery disease or concomitant Valvular disorders had the C-port device employed to construct an end to side distal coronary artery anastomosis by attaching a segment of reverse saphenous vein graft to coronary artery with 50% or more proximal narrowing. In isolated CABG patients the distals were done either off-pump or as a pump- case depending upon surgeon preference. The target arteries were assist assessed for presence of calcification a clear contraindication. The coronary diameter range was 1.0 to 2.5mm. Reverse greater saphenous vein was suitable if it was between 4 and 6 mm in diameter and had a wall thickness less than 1.4mm. Graft flows were checked at the end of each procedure. Patients were monitored post op for myocardial infarction. Results. The C-port device was deployed 76 times in 51 patients. 4 times (5.3%) the deployment was unsatisfactory and the anastomosis had to be redone hand sewn. I time (1.3%) the device failed to fire completely and a new device was used successfully. Total device initial failure rate of 6.6%. With failure no coronary artery appeared harmed and a hand-sewn anastomosis was constructed as usual. There have been no acute coronary events either MI, stroke or death to date in the early postoperative period. CT Angiography is planned on specific study patients at 6 months post-op.

**Conclusion**. The Cardica C-Port distal anastomotic device has been successfully deployed in 71 out of 76 firings on 51 Opcab, Pump-assist and

Cabg/valve patients with careful coronary artery and saphenous vein selection. Immediate patency appears acceptable and further close evaluation is clearly indicated.

### HOSPITAL MORTALITY IN PATIENTS WITH PREOPERATIVE RENAL DYSFUNCTION UNDERGOING CARDIAC SURGERY

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**Introduction.** Patients with renal dysfunction prior to surgery have an increased risk of morbidity and mortality postoperatively. We attempted to identify factors associated with poor outcomes in this high risk group.

**Methods.** This was a retrospective chart review from 2000-2003 of all cardiac surgical patients who were identified as having renal dysfunction prior to their procedure (about 12% of total population). Preoperative, intraoperative and postoperative data were collected and compared to in-hospital mortality. **Results.** There were 312 patients identified with renal dysfunction. The inhospital mortality rate was 14.4%. Patient data is shown in Table 1. Using multivariate analysis, we found that the use of Epogen and dialysis were significant predictors of mortality. We then stratified by preoperative use of dialysis (Table 2). Thus, for patients not on dialysis, the use of epogen was associated with a 3 fold increase in death (95% CI: 0.71-12.29).

**Conclusion.** For patients with renal dysfunction who are on dialysis, postoperative mortality rates were high regardless of Epogen use. For patients not on dialysis prior to surgery, the use of Epogen appears to be associated with an increased risk of adverse postoperative outcomes and mortality.

No Death Hospital Deat		ath	p-value	
13.0%	31.0%		0.006	
14.2%	33.3%		0.004	
36.0%	52.4%		0.05	
40.0 (±28)	36.4 (±	±4I)	0.48	
6.4%	15.6%		0.06	
1.9%	26.7%		< 0.001	
0.4%	11.1%		< 0.001	
15.4 (±20)	33.I (±	±29)	0.01	
Mortality if not on dia	alysis pre-op	Mortality	y if on dialysis	pre-op
26/245 (10.6%)		3/10 (30.0%)		
4/14 (28.6%)		9/33 (27.3%)		
	13.0% 14.2% 36.0% 40.0 (±28) 6.4% 1.9% 0.4% 15.4 (±20) Mortality if not on dia 26/245 (10.6%	13.0%     31.0%       14.2%     33.3%       36.0%     52.4%       40.0 (±28)     36.4 (±       6.4%     15.6%       1.9%     26.7%       0.4%     11.1%       15.4 (±20)     33.1 (±       Mortality if not on dialysis pre-op     26/245 (10.6%)	13.0%     31.0%       14.2%     33.3%       36.0%     52.4%       40.0 (±28)     36.4 (±41)       6.4%     15.6%       1.9%     26.7%       0.4%     11.1%       15.4 (±20)     33.1 (±29)	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$

# REDUCED INCIDENCE OF STROKE IN CABG PATIENTS WITH THE GUIDANT HEARTSTRING PROXIMAL ANASTOMOTIC DEVICE

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Introduction. Stroke associated with coronary artery bypass surgery is felt to be most likely produced intra-op from ascending aortic emboli released during aortic cross clamping or side-biting. This retrospective study looks at the incidence of neurologic complications following isolated CABG procedures were all proximal aortic anastomosis were constructed with the Heartstring device. No side biting or cross clamp was applied to the patients aorta. **Methods.** From January 2005 till April 2006 157 consecutive patients with isolated CABG procedure had all of their 390 proximal anastomoses performed with the Heartstring device (2.5 proximals/patient). All patients had transesophaeal/Epi-Aortic echo and digital palpation of their aorta performed. 78 patients were done as strict OPCAB and 79 were done as Pumpassist (On cardio pulmonary bypass, kept warm, no arrest). All proximals were done off-pump with systolic Bp kept at 80 to 90 mmHg and sewn with 6-0 prolene. Bypass patency was assessed by intraoperative flow measurements. Patients were monitored and followed for neurologic events, graft occlusion and MI. If the patient had a history of CVA, preop head CT scans were obtained as baseline.

**Results**. There were 3 conversions of planned OPCAB to pump-assist for hemodynamic reasons and 2 conversions of Pump-assist to OPCAB (planned pump assist changed to OPCAB due to aortic calcific plaque) Eight devices developed cracks in their seal during loading and had to be replaced. No patient had to have a side-biting clamp applied and no aortic dissections occurred. No perioperative ischemic events occurred and there were no postoperative neurologic complications. Four OPCAB patients returned within 3 months with chest pain. Angiography demonstrated 7 graft occlusion, 3 total graft/4 mid to distal graft stenosis (all in diabetics with poor distal targets). One Pump-assist patient had 2 graft failures, 1 complete/1 mid graft stenosis. There was a total of 9 graft failures (2.3%).

**Conclusion.** The Heartstring device allows for a reliable and safe proximal anastomosis to be performed with no stent material left behind. Patency rates are acceptable and stroke was avoided in both OPCAB and Pumpassist cases. Patency rates appear better with Pump-assisted cases.

# HIGH-DOSE ATORVASTATIN IMPROVES IMPAIRED CEREBRAL VASOMOTOR REACTIVITY

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**Introduction.** Vasomotor reactivity (VMR) describes the dilatory and constrictive response of cerebral resistance vessels to vasoactive stimulation. An impaired VMR is associated with hypertension, subcortical white matter lesions and lacunar infarction. Endothelial dysfunction is ameliorated by statin therapy. The influence of statin therapy on cerebral vasomotor function has yet to be fully characterized. We here report the effects of high dose atorvastatin therapy on cerebral vasoreactivity.

**Methods.** We prospectively enrolled 36 patients with controlled hypertension and LDL cholesterol >100mg/dl. Patients with cortical infarction on brain MRI and large vessel stenosis by extracranial Duplex and transcranial Doppler were excluded. All patients were treated with atorvastatin 80mg daily for 6 month. VMR was measured by  $CO_2$  inhalation and hyperventilation in the bilateral middle cerebral arteries (MCA) at baseline, 3 and 6 month of therapy. Therapy was then discontinued and all patients were retested 7.5 months after study onset. Blood pressure, lipid profile, liver function panel and creatine kinase levels were regularly monitored.

**Results.** Mean age of patients was 60 years, 17 were men 12 had a prior history of subcortical cerebral infarction. Mean LDL cholesterol prior to treatment was 154  $\pm$  30 mg/dl. Atorvastatin lowered LDL cholesterol by 43% and 35% at 3 and 6 months respectively. Baseline VMR was 70  $\pm$  20% bilaterally. There was no significant effect of atorvastatin on VMR at 3 and 6 months across the entire study population. In 17 patients pre-treatment VMR was impaired, defined as <70%. In that subgroup of patients atorvastatin lead to significant improvement of VMR at 3 and 6 months by 20% and 17% respectively. **Conclusion.** High dose atorvastatin significantly improved impaired cerebral vasomotor reactivity. We found no benefit of atorvastatin therapy in patients with preserved baseline vasoreactivity. The beneficial effects of atorvastatin of cerebral vasoreactivity may in part explain the neuroprotective properties attributed to statin therapy.

# THE PRACTICE OF CARDIOPULMONARY BYPASS—REDUCING THE GAP BETWEEN INTUITION AND EVIDENCE

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**Introduction.** Evidence-based guidelines regarding the practice of cardiac surgery have been in the literature for more than a decade, and continue to be refined in wake of new and emerging evidence.<sup>1</sup> Previous attempts at synthesizing the evidence base of cardiopulmonary bypass (CPB) have selectively reviewed the cardiac surgery literature, and have not involved all members of the clinical team, most notably perfusionists.<sup>2.3</sup> This gap in knowledge of the literature is in stark contrast with the shared goal of the cardiac team, namely to improve the conduct of CPB to reduce the patient's risk of adverse outcomes secondary to cardiac surgery and CPB.

**Methods.** We adopted a process set forth by the American Heart Association (AHA) and American College of Cardiology (ACC) for the development of evidence-based reviews of the peer-reviewed literature. Critical to the success of this project was a detailed and thorough literature search conducted by an expert biomedical librarian. Searches were conducted for each of the agreed-upon topics, and results posted on a customized website through the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/entrez/). Expert reviewers accessed the saved searches through this website and developed the findings contained herein. Findings were shared with all co-investigators, and reflect input gathered from presentations at regional, national and international conferences. The authors then graded the level of evidence and classified the findings listed below based on the criteria published by the AHA/ACC. **Results** 

### Neurological Protection

pH Management: The clinical team should manage adult patients undergoing moderate hypothermic CPB with alpha-stat pH management. (Class I, Level A). Avoidance of Hyperthermia: Limiting arterial line temperature to 37°C may be useful for avoiding cerebral hyperthermia. (Class IIa, Level B). \*Coupled temperature ports for all oxygenators should be checked for accuracy and calibrated.

Minimizing Return of Pericardial Suction Blood: Direct reinfusion to the cardiopulmonary bypass circuit of unprocessed blood exposed to pericardial and mediastinal surfaces should be avoided. (Class I, Level B). Blood cell processing and secondary filtration may be considered to decrease the deleterious effects of reinfused shed blood. (Class IIb, Level B).

Aortic Assessment: In patients undergoing cardiopulmonary bypass at increased risk of adverse neurological events, strong consideration should be given to intraoperative TEE or epiaortic ultrasound scanning of the aorta: (1) to detect nonpalpable plaque (Class I, Level B); (2) for reduction of cerebral emboli (Class IIa, Level B).

Arterial Filtration:Arterial line filters should be incorporated in the CPB circuit to minimize the embolic load delivered to the patient. (Class I, Level A). Maintenance of Euglycemia. The clinical team should maintain perioperative blood glucose concentration within an institution's normal clinical range in all patients including non-diabetics. (Class I, Level B).

Reduction of Hemodilution. Efforts should be made to reduce hemodilution including reduction of prime volume in order to avoid subsequent allogenic blood transfusion. (Class I, Level A)

Attenuation of the Inflammatory Response: Reduction of circuit surface area and the use of biocompatible surface modified circuits may be useful/effect at attenuating the systemic inflammatory response to cardiopulmonary bypass, and improve outcomes. (Class IIa, Level B).

**Discussion.** We have made every effort to develop findings for CPB practice that are grounded in evidence-based medicine. We adopted a previously validated method for explicitly reviewing and grading the level and class of evidence as it relates to neurological injury, euglycemia, hemodilution, and the inflammatory response. These findings will be updated on a routine basis, including the addition of other practice items, to keep them contemporaneous with the peer-reviewed medical literature and useful and pertinent to practicing clinicians.

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# CARDIOPULMONARY BYPASS GUIDELINES IN ADULTS: THE NORTHERN NEW ENGLAND EXPERIENCE

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**Introduction.** Clinical practice guidelines exist to assist clinicians in the choice of therapeutic technique to meet the needs of the patients that they serve. Often these documents are thought of as resources, and are not used concurrently with care. Recently, guidelines for the practice of cardiopulmonary bypass in adults undergoing moderate hypothermia were developed. We sought to evaluate current clinical practice in reference to new guidelines within the northern New England region.

**Methods.** We examined the practice of cardiopulmonary bypass at eight medical centers within the northern New England region from January 2004 – June 2005 (n=3,597 patients). We operationalized each of the eight guide-lines by identifying variables within our prospective registries which described the practice of cardiopulmonary bypass (CPB) in each statement. We describe regional practice (min, max by center) for each guideline.

**Results**. We were able to operationalize fully all but one guideline statement using our regional registries. All centers used alpha-stat pH management and

arterial line filters in this population, but wide variation existed among other guideline statements. Avoidance of hyperthermia (blood temperature <37 degrees) occurred during 23.4% of procedures (1.5%, 83.2%). Maintenance of blood glucose level at <200mg/dL was achieved in 82.7% (57.1%, 97.9%) of procedures. Cardiotomy suction was not used during 25% of procedures (1%, 94%). Processing of shed blood with a cell saver occurred among 60.4% of procedures (6%, 99%). Aortic assessment with transesophageal or epiaortic echocardiography occurred among 73% of procedures (1%, 99%). Median static volume was 1600ml (900ml, 1760ml), and median lowest hematocrit on CPB was 23% (22%, 25%). The use of at least a partially coated circuit occurred among 84% of procedures (9%, 100%).

**Conclusion**. We operationalized new CPB guidelines, and subsequently used our regional prospective perfusion registry to assess practice within our region as it relates to these guidelines. Tracking performance as it relates to these guidelines will be important for understanding and reducing variation in clinical practice as it relates to evidence-based medicine.

# THE MINIMIZED, EXTRACORPOREAL CIRCULATION SYSTEM (IDEAL) IS SAFE AND COST EFFECTIVE

Arndt-H. Kiessling, Frank Isgro, Martin Lange, Kai-Uwe Kretz, Andreas Lehmann, Werner Saggau

**Background.** Target of our investigation was the measurement of cognitive and neurological status after CABG surgery using a minimized extracorporeal circulation system.

Methods. The study was carried out as a prospective, randomised clinical trial involving 50 patients undergoing elective CABG surgery. The patients were randomly divided into two subgroups (25/25). IDEAL (Sorin-Group, Italy) was used in one subgroup compared to a standard closed system. Due to a reduced priming volume (800 ml), the aprotinin dose was halved in the IDEAL group (integral centrifugal pump, oxygenator and arterial filter). Various blood parameter of the coagulation system and markers of the inflammatory response were collected pre-, intra- and postoperative. Pre- and on the sixth postoperative day, a bedside neuropsychological test battery (Beck's Anxiety Inventory, D2 test, Trail Making Test, MMSE and Benton test) was performed. Results. Demographic data and clinical outcome was identical in both groups. There were no statistically significant differences in concentrations of C3a, interleukin 6, procalcitonin, F XII, F XIII, amount of blood loss and need for donor blood. The neuropsychological test results deteriorated after the cardiac procedure, but show no differences between the two groups. The IDEAL system worked without technical disorders. During cardiac dislocation for anastomosis of marginal branches, a sufficient volume preloading is necessary.

**Conclusion.** A minimized extracorporeal circulation system can be applied safely in CABG patients. A halved dose of aprotinin had no effects on the postoperative blood-loss. A compact and space saving system correspond with today's demand of modern perfusion technologies in conjunction with improved cost effectiveness.

### PROLONGED OXIDATIVE STRESS LEVELS CONNECTED TO NEUROLOGIC INJURY AFTER CARDIOPULMONARY BYPASS

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Introduction. Neurocognitive decline(NCD) is a common complication in cardiac surgical patients. Its pathophysiology remains unknown; leading to significant morbidity particularly in the elderly. We studied the levels of oxidative stress, leukocyte adhesion molecules and markers of central nervous(CNS) injury in relation to NCD in patients following cardiopulmonary bypass (CPB).

**Methods.** Prospective cohort of low-risk forty two patients undergoing CABG and/or valve procedures using cardiopulmonary bypass were administered a neurocognitive battery prooperatively, postoperatively at day 4 (POD4) and at three months. Battery consisted of eight validated assessments covering memory, executive function, naming, attention, fluency and premorbid intelligence. Following published Consensus Statement Guidelines, NCD was defined as one standard deviation from baseline on  $\geq$ 25% of tasks. Leukocyte adhesion molecules sICAM and sVCAM were quantified from serum with high sensitivity immunoassay. CNS injury was assessed through increase in levels of serum axonal Tau protein (dichotomous variable) and s1008 protein. Total peroxide levels were quantified as a measure of oxidative stress. Analysis of Variance (ANOVA), logistic regression, Mann-Whitney and Spearman Correlation were used for statistical analysis where appropriate.

**Results**. Cohort studied had an NCD rate of 40.4% (17 of 42) with a mean age 72±3.6 years. Baseline characteristics and known predictors of NCD

such as age, education level and perioperative temperature were not significantly different between patients with/without NCD. Oxidative stress, sICAM and markers of CNS injury were significantly more elevated following CPB in patients with NCD compared to patients without NCD as described in table below. Moreover, NCD patients had a prolonged elevation that persisted until the POD4 measurement. sVCAM was not found to be significant in this study.

**Conclusion**. NCD following CPB is associated with elevations in markers of axonal CNS injury after surgery. Particularly, oxidative stress and inflammatory mediators play a key role in NCD pathophysiology, and could become a target for prevention.

Marker	NCD Group Mean $\pm$ SEM	No NCD Group Mean±SEM	p-Value
Total Peroxide	Inte	r-group effect	0.01
NSE	Inte	r-group effect	0.027
Tau Protein (% Increase)	78%	27%	0.024
sICAM — ng/ml (POD4)	660.4±28.3	516.6±62.5	0.028
sVCAM — ng/ml (POD4)	1005±139.7	1078±147.7	NS

# RECOMBINANT APROTININ VARIANTS, BUT NOT TRANEXAMIC ACID, BLOCK PLATELET ACTIVATION VIA PARI

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**Introduction.** Thrombin generated during cardiopulmonary bypass activates the high affinity thrombin receptor, protease activated receptor (PAR)I, causing platelet activation and dysfunction. The serine protease inhibitor aprotinin is a hemostatic agent used to reduce transfusion requirement in cardiac surgery through an antifibrinoytic mechanism. However, compared to other categories of antifibrinolytic agents (e.g. the lysine analog tranexamic acid) aprotinin may confer additional patient benefit by protecting platelets against thrombin mediated PARI activation. Here we have tested the hypothesis that aprotinin and its recombinant analogues (arginine-15, arginine-15-alanine-17 and valine-15-leucine-17) but not tranexamic acid can block PARI mediated platelet aggregation *in vitro*.

**Methods.** Aggregation studies were carried out using washed human platelets (n=9) or platelet rich plasma (n=7) from healthy volunteers activated with 1 or 5nM thrombin. Recombinant aprotinin variants were used at the molar equivalent to 50 KIU/ml of the parent compound. Tranexamic acid was used at 10mg/ml. The PAR1 antagonist peptide FLLRN was used at 500 $\mu$ M.

**Results.** Platelet aggregation at low concentrations of thrombin (1nM) was mediated exclusively via PAR1. At this concentration of thrombin, the mean percentage +/- S.D. aggregation of washed platelets was  $68.6 \pm 12.3\%$ . This was suppressed by each aprotinin variant at the 50 KIU/ml equivalent dose: arginine-15 (23.0 ± 17.5%, p<0.001); arginine-15-alanine-17 (33.3 ± 22.9%, p<0.01); aprotinin (37.5 ± 19.4%, p<0.05); valine-15-leucine-17 (50.0 ± 16.1%, not significant). In contrast, tranexamic acid had no significant effect on platelet aggregation (p=0.231). At 5nM thrombin, which activates both high (PAR1) and low affinity (PAR4) thrombin receptors on platelets, FLLRN and aprotinin failed to block aggregation: this indicates that aprotinin selectively targeted PAR1. Similar results were obtained in platelet rich plasma, with aggregation at 1 nM thrombin of 77.1 ± 10.0%; this was inhibited in the order: arginine-15 (30.1 ± 9.6%, p<0.001); arginine-15-alanine-17 (52.3 ± 9.7%, p>0.001); aprotinin (55.9 ± 6.2%, p>0.001); valine-15-leucine-17 (73.7 ± 7.1%, not significant).

**Conclusion.** Aprotinin variants arginine-15 and arginine-15-alanine-17 inhibit PAR1 mediated platelet aggregation. However, tranexamic acid and aprotinin variant valine-15-leucine-17 do not. With more understanding of the mechanisms of action of aprotinin and its derivatives, safer and more efficacious aprotinin variants may become available for clinical use.

### APROTININ INHIBITS ENDOTHELIAL CELL PPRODUCTION OF MONOKINE INDUCED BY GAMMA INTERFERON (MIG/CXCL9 CHEMOKINE): IMPLICATIONS FOR NEUROPROTECTION AND LIVER TRANSPLANTATION

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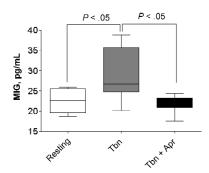
**Introduction.** MIG/CXCL9 is a chemokine expressed in liver and brain during inflammation. It specifically chemoattracts CXCR3+ lymphocytes to rejecting liver transplants and astrocytes to the infarct area in stroke. Aprotinin (Trasylol) is a serine protease inhibitor with reported neuro-

protective properties when used in cardiac surgery with cardiopulmonary bypass and improved graft survival when used in orthotopic liver transplant surgery. Here we have addressed the hypothesis that: 1) thrombin can upregulate MIG/CXCL9 expression in endothelial cells and 2) aprotinin can block this.

**Methods.** Cultured human umbilical vein endothelial cells were stimulated with thrombin at 0.15 u/ml in the presence and absence of aprotinin at 1600 kiu/ml. MIG/CXCL9 levels in culture supernatants were measured by a customized protein array (Raybiotech) and by ELISA analysis (R&D Systems).

**Results**. Out of 48 human cytokines and chemokines screened by proteins, array, MIG/CXCL9 was the most highly differentially expressed molecule (> 7 fold induction) in the presence of thrombin. ELISA analysis shown in the attached figure demonstrates elevated concentrations of MIG/CXCL9 in culture supernatants following stimulation with thrombin (P<0.05) but significant inhibition in the presence of aprotinin (P<0.05).

**Conclusion**. These studies present the first evidence that MIG/CXCL9 is differentially induced in endothelial cells in the presence of thrombin; furthermore, aprotinin significantly inhibits this. Additional work will be required *in vivo* to confirm the clinical relevance of these observations, but they provide a mechanistic framework to explain the neuroprotective properties of aprotinin and enhanced graft survival following orthotopic liver transplantation.



### A METHOD TO REDUCE ALLOGENEIC BLOOD EXPOSURE AND HOSPITAL COSTS WHILE PRESERVING CLOTTING FACTOR CONCENTRATION AFTER CARDIOPULMONARY BYPASS.

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**Introduction.** Recent data linking allogeneic blood use to increased morbidity and mortality after cardiopulmonary bypass (CPB) warrants the study of new methods to reduce allogeneic blood exposure and preserve proteins and clotting factors after CPB. The Hemobag<sup>(r)</sup> technology allows the openheart team to safely concentrate the residual CPB circuit contents and quickly return a high volume of clotting factors and blood cells back to the patient.

**Methods.** After IRB approval in a community hospital setting, sixty-six (66) patients were randomly selected to receive the Hemobag<sup>(r)</sup> (HB) therapy. A concurrent control group of 66 non-Hemobag<sup>(r)</sup> (NHB) patients were matched to the HB group patient-by-patient according to surgeon, procedure, age, BSA, Body weight and CPB time. Techniques to conserve blood, the Cell Saver<sup>(r)</sup> and pre-CPB whole blood sequestration (ANH), were employed in both treatment groups. Post-CPB cell-washing of the bypass circuit contents was additionally employed in the control (NHB) group.

**Results**. There were no significant differences between the two groups in regard to patient morphology, pre-op cell concentrations, distribution of surgeons and procedures, pump and ischemic times, or risk scores. The average HB volume returned to the patient was 852 +/- 197 ccs (1 SD). The HB contained an average platelet count of 238 +/- 73 K/mm<sup>3</sup>, fibrinogen concentration of 451 +/- 174 mg/dl, total protein of 8.2 +/- 1.9 gm/dl and hematocrit of 44 +/- 6 %. Factor VII levels in three HB contents averaged a 259% increase. HB patients received significantly less RBC transfusions, experienced lower ventilator times, had a higher hematocrit nadir, and higher postop platelet counts. Total donor exposures per patient and the cost of the blood products were lower in the HB group.

**Conclusion**. Infusion of the CPB circuit residual blood concentrate appears to safely recover proteins, clotting factor and cell volume for all types of cardiac procedures which leads to reduced patient donor exposures, improved outcomes and reduction in the related costs.

### MEASUREMENT OF AORTIC STRAIN AND PLAQUE BURDEN: CORRELATION WITH AORTIC FLOW VELOCITY DURING CARDIOPULMONARY BYPASS

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**Introduction.** Aortic plaque burden has been demonstrated to increase the risk of stroke during cardiac surgery. Recently, pulse wave pressure, a measure of wall stiffness, has been demonstrated to be associated with increased mortality in patients over 70, diabetics and those with essential hypertension. The purpose of this prospective observational study was to examine the relationship between aortic plaque, aortic stiffness and pump flow velocity during CPB.

Methods. Patients undergoing cardiac surgery had echocardiographic measurements of aortic plaque, aortic stiffness (Ep and Beta), and blood flow velocity in the aortic arch during CPB (pump flows 2.4 l/m2). In addition, the change in creatinine, occurrence of stroke, and occurrence of MI were recorded postoperatively.

**Results**. To date, 22 patients undergoing cardiac surgery have been enrolled. These included 6 females and 16 males with a mean age of 63.2(9). Nine of 22 patients had ascending aortic plaque mean 2.0 mm (0.8), 15 of 22 patients had arch plaque mean 1.2 mm(0.7) and 21 had descending plaque mean 1.5 mm (SD 1.5). Ep mean was 1054 dynes/cm2 (SD 676 dynes cm2) and beta index was 4 (0.487). Mean aortic flow velocities were 3.6 m/sec2 (SD 1.4). In all but 2 cases pump flow was directed along the lesser aortic curvature. While scatter plots suggested a relationship between Age and both plaque burden and aortic stiffness (Ep and beta), this was not significant. There was no significant correlation with pump flow and BSA, plaque burden, Ep or beta. When separated by plaque burden there was a significant difference in Beta in patients with ascending aortic plaque greater than 1.5 mm (3.8 vs 3.4 p=0.04). but no difference in Ep or Beta for plaque within the arch or descending aorta.

**Conclusion**. Measurements of Ep and beta are easily performed in cardiac surgical patients.

### CLINICAL EVALUATION OF THE A-VIEW METHOD: A NEW DIAGNOSTIC METHOD FOR VISUALIZING THE ASCENDING AORTA IN PATIENTS UNDERGOING CARDIAC SURGERY.

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**Introduction.** Transesophageal echocardiography (TEE) prior to sternotomy is unable to detect atherosclerosis in distal AA due to the "blind" spot. A new method (A-View(r) method, extension of TEE) enables assessment, preoperatively, of AA-atherosclerosis using a fluid-filled balloon catheter. Before introducing a new diagnostic test in clinical practice a phased scientific approach is recommended. The aim of this diagnostic study was to evaluate if the A-View(r) method enables visualization of distal AA and safety of the diagnostic.

**Methods.** In a cross-sectional diagnostic trial; patients undergoing cardiac surgery by sternotomy underwent TEE, the A-View(r) method, EUS, and routine operative monitoring. Primary outcome was if the distal AA, i.e. distal from the right pulmonary artery, could be visualized. Secondary outcomes were cardiopulmonary side-effects, bronchial or tracheal damage, and the presence and severity of atherosclerosis.

Frequencies of visualizing the distal AA with TEE and with the A-View(r) method, and adverse effects related to the A-View(r) catheter were quantified. The degree of agreement in determining atherosclerosis between A-view(r) method and EUS was estimated using Kappa-statistic.

**Results.** Study population consisted of 41 consecutive patients, 28 (68.3%) males and 13 females (31.7%), mean age 67 years ( $\pm$  11 years). With A-View(r) method the distal AA was visible in all (100%) patients. There were no clinical significant side-effects associated with the use of the A-View(r) catheter. In 7 (18%) patients bronchoscopy revealed insignificant mucosal bleeding, this required no additional interventions nor delayed planned surgery. Severity of atherosclerosis visualized with A-view(r) method compared to EUS results showed a Kappa of 0.69 (0.50 -0.88).

**Conclusion.** The A-View(r) method offers an easy, safe, and minimally invasive approach of visualizing the distal AA. Compared to EUS, the A-View(r) method yielded adequate results in the detection of AA atherosclerosis. The

technique can be used prior to sternotomy. Therefore, surgical strategy can still be adjusted to reduce manipulation of the AA in case of aortic atherosclerosis. Accordingly, the A-View(r) method seems a promising tool for patients undergoing cardiac surgery to reduce post-operative stroke. Formal studies on the inter- and intra observer variance and on the diagnostic accuracy of the A-view(r) method are planned.

# EPIAORTIC SCANNING MODIFIES SURGICAL MANAGEMENT IN CABG SURGERY

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**Introduction.** Atherosclerosis of the ascending aorta and aortic arch is one of the most significant risk factors for perioperative stroke.<sup>1,2</sup> Our purpose was to determine if *epiaortic scanning* altered surgical management in patients at high risk of neurological injury undergoing CABG surgery.

**Methods.** After REB approval, consent was obtained from 113 patients > 70 years scheduled for elective CABG surgery. Patients were randomized to Epiaortic group (aortic manipulation of the proximal thoracic aorta, guided by epiaortic scanning and TEE) or Control group (guided by TEE and manual palpation by the surgeon). Aortic atheroma was graded on a four-point scale, normal (0), mild (1), moderate (2), or severe (3).<sup>3</sup> Real-time TEE findings were conveyed to the surgeons who were free to modify operating technique and apply ultrasound for aortic manipulation. TCD was used to monitor middle cerebral artery. Neurological assessment was done with NIHSS and NEECHAM confusion scale.

**Results**. There were no differences in baseline demographic data and surgical characteristics between Epiaortic (n = 55) and Control (n = 58) groups. Grade I atheroma of the ascending aorta was detected more in Epiaortic group compared to Controls (13% vs 5%, p=0.03). 7 patients from Control group crossed over to Epiaortic group prior to aortic cannulation. Intraoperative surgical management was changed in 16 patients in the Epiaortic group and 7 patients in the Control group, p=0.025. (Table) There was no significant difference in TCD embolic count, NIHSS scores, or perioperative morbidity and mortality between groups. Compared to baseline, NEECHAM scores were considerably worse during the first three postoperative days in both groups. **Discussion.** This study confirms that epiaortic scanning results in modification of aortic cannulation sites and alterations of intraoperative surgical management in elderly patients at high risk of neurological injury undergoing CABG surgery.

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Comparison of changes in planned operative surgical management

	Epiaortic (N=55)	Control (N=58)	Р
OPCAB	(1.8)	l(1.7)	.95
Distal arch cannulation	3 (5.4)	l (1.7)	.28
Fib Arrest (no x clamp)	2 (3.6)	l (l.7)	.53
Adjustments- cannulation site			
in ascending aorta	10 (18)	4 (6.9)	.07
Total	16 (29)	7 (12)	.025

# HIGH INTENSITY TRANSIENT SIGNALS: VENOUS AIR ENTRAINMENT $\rightarrow$ ARTERIAL OUTFLOW $\rightarrow$

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**Introduction.** We have previously reported the development and implementation of a multi-monitoring modality to identify the association between processes of clinical care and mechanisms creating neurologic injuries. In this current study, we report the association between embolic signals (HITS) entering and exiting the cardiopulmonary bypass circuit (CPB) and HITS detected in the cerebral arteries.

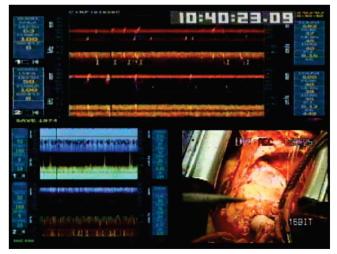
**Methods.** We enrolled 121 patients in a prospective cohort study at a single medical center from 10/30/2005 to 2/9/2006. Eight-six percent of these patients underwent isolated coronary artery bypass grafting (CABG), while the remaining underwent valve surgery with or without CABG. Both cerebral and CPB were monitored using the Spencer Technologies Power M-Mode Doppler (Tustin, CA). Simple linear regression was used to quantify the association between HITS detected in the CPB circuit and those detected in the cerebral arteries. Separate regression models were used to

investigate both the relationship between source of CPB embolic activity (inflow vs. outflow) and cerebral HITS and procedure type. Models were assessed through the R-squared value, namely the percent of the variation in cerebral HITS accounted for by variables included in the model.

**Results**. Median cerebral, CPB venous inflow and CPB arterial outflow HITS were higher among valvular vs. coronary surgeries (p = 0.00). HITS stemming from CPB arterial outflow were more predictive of cerebral HITS than CPB venous inflow HITS. In our experience, the predominant source of outflow HITS was CPB venous inflow HITS (see picture below). Seventeen percent of the variation in cerebral HITS was accounted for by CPB inflow HITS (1% among coronary patients, and 59% among valve patients). Thirty-two percent of the variation in cerebral HITS was accounted for by CPB outflow HITS (7% among coronary patients, and 81% among valve patients).

**Conclusion**. HITS detected in the CPB circuit are a significant contributor to HITS detected in the cerebral arteries. This association was more pronounced on the arterial vs. venous side of the CPB circuit, and among valve vs. coronary patients. These HITS are most likely gaseous in constitution. Efforts to reduce cerebral HITS should focus on reducing air entrainment into the venous line of the CPB circuit.

Note on picture: Air noted entering venous line (top band, bottom left quadrant), subsequently in arterial side (bottom band, bottom left quadrant), and then in brain (top two bands, top quadrant).



Ability	of	HITS	Detected	in	CPB	to	Predict	HITS	Detected	in	Cerebral	Arteries	

Variable	p-value	K-squared*	
CBP Inflow	0.06	17%	
Valvular Operation	0.00		
CBP Outflow	0.00	32%	
Valvular Operation	0.12		
CBP Inflow	0.38	1%	
CPB Outflow	0.01	7%	
CPB Inflow	0.00	59%	
CPB Outflow	0.00	81%	
	CBP Inflow Valvular Operation CBP Outflow Valvular Operation CBP Inflow CPB Outflow CPB Inflow	CBP Inflow 0.06 Valvular Operation 0.00 CBP Outflow 0.00 Valvular Operation 0.12 CBP Inflow 0.38 CPB Outflow 0.01 CPB Inflow 0.00	

\*R2: Percent of variation in cerebral emboli accounted for by each model. CPB = cardiopulmonary bypass.

### DIAGNOSTIC PROPERTIES OF THE WRITTEN PAPER RECORD— MISSED OPPORTUNITIES

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**Introduction.** Hypotension during cardiopulmonary bypass has previously been associated with adverse sequelae. We sought to estimate the diagnostic properties (i.e., sensitivity and specificity) and accuracy of the anesthesiologists' and perfusionists' recording of hypotension during cardiopulmonary bypass by comparing it to the computerized record, which served as our gold standard. **Methods.** We enrolled 73 patients in a prospective cohort study at a single medical center from 10/30/2002 to 7/22/2005. We collected mean arterial

pressure (MAP) values during cardiopulmonary bypass from the computerized record, and written records (anesthesia and perfusion). The former captured MAP ever 20 seconds throughout the entire case. The latter were recorded at 10-minute intervals. For each 10-minute interval, we defined the gold standard as indicating hypotension if the computerized record indicated hypotension during at least 5 of the 10 minute interval. Sensitivity and specificity (with 95% CI) were estimated using generalized estimating equations for binary endpoints to account for repeated observations from the same patient. Concordance of identifying hypotension between each record was calculated with a Kappa statistic.

**Results**. Data on 943 ten-minute intervals from 73 operations was analyzed. The incidence of hypotension was 5.0% by the computerized record, 5.4% by the perfusion record, and 4.4% by the anesthesiologist record. The sensitivity and specificity of the written perfusion record as it relates to the computerized record was 28% (14, 48) and 96% (95, 98), respectively. The sensitivity and specificity of the written anesthesia record as it relates to the computerized record was 4% (1, 17) and 95% (92, 97), respectively. There was *poor* agreement between the anesthesia and computerized records (Kappa -0.01), *slight* agreement between the perfusion and anesthesia records (Kappa 0.19), and *fair* agreement between the perfusion and computerized records (Kappa = 0.28).

**Conclusion**. The sensitivity of both the written perfusion and anesthesia record for detecting hypotension during cardiopulmonary bypass was low, although the specificity was quite high. The perfusion record had more favorable diagnostic properties and higher concordance with the computerized record than the anesthesia record. These findings have implications for both research and quality improvement initiatives. The written records may not allow one to appreciate and understand the variation in blood pressure and other important hemodynamic parameters during cardiopulmonary bypass. Efforts should be made to transition away from the paper to a permanent computerized record system.

Sensitivity and Specificity of Written Records to a Computerized Record System

	Sensitivity	95% CI	Specificity	95% CI
Perfusion	28%	(14, 48)	96%	(95, 98)
Anesthesia	4%	(1, 17)	95%	(92, 97)

# MEAN ARTERIAL PRESSURE AND WATERSHED STROKES IN CARDIAC SURGICAL PATIENTS.

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**Introduction.** The incidence of watershed strokes in cardiac surgical patients is higher than in the general stroke population, but the mechanism is poorly understood. We sought to determine whether the change in mean arterial pressure from before surgery to during surgery affected the development of watershed strokes.

**Methods.** From 1998-2003 we studied 98 patients with a clinical diagnosis of stroke following cardiac surgery who underwent MRI with diffusion-weighted imaging (DWI). We then retrospectively identified patients with bilateral watershed infarcts and examined the change (from preoperative to intraoperative) in mean arterial pressure (MAP) level. We examined three MAP parameters: preoperative MAP, average intraoperative MAP (while on cardiopulmonary bypass), and drop in MAP (the average intraoperative MAP subtracted from the preoperative MAP).

**Results.** Bilateral watershed infarcts were seen in 48% of patients who had DWI. Patients with bilateral watershed infarcts were more likely to have undergone an aortic procedure and less likely to have undergone CABG (p=0.04), and have longer cardiopulmonary bypass times (p=0.02). Patients with a drop in MAP (of 10 mmHg or more) were 2.8 times as likely to have had a watershed infarct than those patients who had a smaller drop in MAP. The odds ratio for having a watershed infarct (compared to other infarct types), after adjustment for preoperative MAP, history of hypertension, and use of intraoperative circulatory arrest was 4.1 (95% CI: 1.1-15.0). There was no association when the average intraoperative MAP and the lowest intraoperative MAP were examined. Patients with a drop in MAP (of 10 mmHg or more) were also 3.9 times as likely to have a larger infarct volume (95% CI: 1.4-10.7).

**Conclusion.** These preliminary data suggest that an important factor in the development of watershed strokes is *change* in mean arterial pressure from baseline, not the absolute intraoperative blood pressure. Thus, future trials to improve neurological outcomes in cardiac surgery patients should take into account comprehensive blood pressure monitoring and analyses.

# EMBOLIC EVENTS ASSOCIATED WITH CARDIOPULMONARY BYPASS DISRUPT THE BLOOD BRAIN BARRIER IN DOGS

D. D. Deal, D. A. Stump, D. M. Moody, W. R. Brown, J. E. Jordan

Wake Forest University Health Sciences, Winston-Salem, NC Introduction. Patients undergoing cardiopulmonary bypass (CPB) receive

a variety of microemboli (gaseous, lipid, particulate atheroma) to the cerebral circulation. Post operative neurobehavioral dysfunction has been linked to embolic events.<sup>1</sup> Microemboli distributed to the brain during CPB also result in a diffuse neurologic injury manifested as a disruption of the bloodbrain barrier (BBB). Breakdown of the BBB possibly explains brain swelling observed by MRI after CPB.<sup>2</sup> We examined the effect of the passage of nonocclusive lipid emboli and occlusive particulate emboli on the BBB.

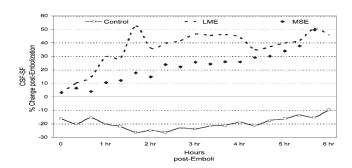
Methods. Anesthetized dogs (≥30kg) received 0.8% sodium fluorescein (SF) IV over a 10-hour period as serum (jugular) and CSF samples (cisterna magna) were collected at 20-minute intervals. The Control group (n=6) had no further intervention. After 3 hours of SF infusion, embolic events associated with CPB were simulated by the infusion of lipid or non-deformable particulate emboli via a cannula placed from the femoral artery into the left ventricle of the heart. The LME group (n=6) received lipid-laden blood (18cc triolein + 350cc blood, well-agitated with air) simulating the return of cardiotomy-suctioned blood. The MSE group (n=4) received 2.5 ×10<sup>6</sup> 15um-diameter microspheres simulating particulate emboli such as friable atheroma. SF levels of all samples were determined using a fluorescent spectrophotometer. Because parametric assumptions could not be satisfied by the CSF-SF values, non-parametric testes were conducted (Friedman test for repeated measures and Kruskal-Wallis One-way ANOVA).

**Results**. Serum-SF levels were similar in all groups, trending to a steady state within 3 hours. Following embolization, CSF-SF levels rose 36-46% in the LME group and 15-57% in MSE group. Both LME and MSE were higher vs. Control at 0-4 hours (p < 0.025), but were not statistically different at 6 hours post-embolization due to the variance within groups.

**Discussion**. Animals receiving emboli showed acute changes in BBB permeability following embolic injury. The length of anesthesia (>10 hrs) and the cumulative CSF sampling (21 mls) may have caused some subjects in the Control group to become unstable after 4 hours post-embolization. These data suggest that embolic events during CPB may contribute to brain edema post-CPB and subsequent decline in neurobehavioral function both acutely and in the long term.

References

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Anesthesiology. 1998; 88(2):340-345.
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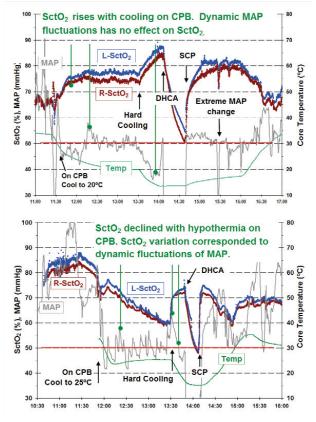


### RESULTS UTILIZING ABSOLUTE CEREBRAL OXIMETRY MONITORING SUGGEST THE NEED FOR TAILORED PATIENT MANAGEMENT DURING CARDIAC SURGERY

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Introduction. Patient management guided by relative change of cerebral oxygen saturation has been shown to improve outcome. An absolute cerebral oximeter that doesn't require baseline recording for data interpretation has been developed recently (FORE-SIGHT<sup>TM</sup>, CAS Medical Systems). We report the preliminary results of a study using this monitor during aortic surgery. **Methods.** Patients undergoing elective thoracic aortic surgery with deep hypothermic circulatory arrest (DHCA) and antegrade selective cerebral perfusion (SCP) were monitored intraoperatively using the FORE-SIGHT monitor. Two sensors were placed on the subject's forehead bilaterally for continuous monitoring of cerebral tissue oxygen saturation (SctO<sub>2</sub>). Results. Post induction SctO2 was 68.5+/-6.0%. During cooling on CPB, a rise in SctO<sub>2</sub> (84.4+/-4.9%) is seen in most subjects. The rate of SctO<sub>2</sub> increase matches the rate of core cooling (usual pattern: 15/17 subjects, Figure Left). During DHCA, SctO<sub>2</sub> decreases to 59.4+/-8.9%, and then returns to pre-DHCA levels during SCP. Unusual SctO<sub>2</sub> patterns in two subjects revealed a failure of SctO<sub>2</sub> to rise with cooling. Echo-cardiography monitoring indicated that the SctO2 decrease in one subject might be caused by air emboli. In the other subject, SctO2 decrease was probably related to the hemodynamic management of the patient. MAP for this subject was maintained around 50 mmHg on CPB, comparable to subjects with normal SctO<sub>2</sub> pattern, post operative analysis shown that, unlike other subjects, SctO<sub>2</sub> variation corresponded to fluctuations of MAP for this patient (Figure Bottom). Discussion. Like others, our findings suggest that patient management on CPB needs to be tailored to the individual patient. Maintaining MAP at 50-60 mmHg during hypothermic CPB is tolerated by most patients, but this level seems to be inadequate for certain patients. The absolute cerebral oximeter could be used as a guide for patient management during cardiac surgery.



# CEREBRAL DESATURATION DURING CABG SURGERY: WHEN IS IT OCCURRING?

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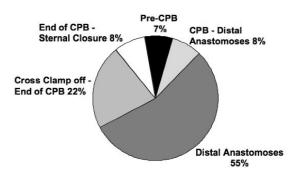
**Introduction.** Previous studies have identified that nearly 10% of strokes in the setting of coronary artery bypass grafting (CABG) surgery associated with cerebral hypoperfusion.<sup>1</sup> Additional research, using near infrared spectroscopy, has identified the contribution of increasing intervals of cerebral desaturation with higher resource utilization. We sought to identify the incidence and timing of cerebral desaturation during isolated CABG surgery.

**Methods.** We enrolled 66 patients CABG patients in a prospective cohort study at a single medical center from 1/7/2003 to 7/26/2005. Cerebral desaturation was measured using near infrared spectroscopy (Somanetics, Troy, Michigan), and defined as at least 1 minute of cererbral desaturation<75% of pre-induction baseline. Processes of care associated with intervals of cerebral desaturation were identified by using a camcorder, which was focused on the surgical site. We divided the procedure into five intervals (pre-CPB,

CPB until the distal anastomoses, duration of the distal anastomoses, Cross Clamp off – end of CPB, end of CPB until sternal closure).

**Results**. Cerebral desaturation was common, occurring among 45/66 (68%) of patients. Most cerebral desaturation occurred during the construction of the coronary artery distal anastomoses (55%), followed by the interval of the cross clamp coming off to the end of CPB (22%), end of CPB to sternal closure (8%), CPB until the distal anastomoses (8%), and pre-CPB (7%).

**Conclusion**. Cerebral desaturation during CABG surgery occurs commonly, during the construction of the distal anastomoses. The most likely mechanism during distal construction is likely cerebral congestion. Communication between team members regarding changes in venous return and other signs of cerebral congestion when positioning the heart may likely prevent these occurrences.



### CLINICALLY SILENT CEREBRAL ISCHEMIC EVENTS AFTER CARDIAC SURGERY: THEIR INCIDENCE, REGIONAL VASCULAR OCCURRENCE, AND PROCEDURAL DEPENDENCE

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**Background.** The reported frequency of stroke after coronary artery bypass grafting varies between 1.5-6%, approaches 10% after aortic valve replacement, and may occur in 40-70% in high risk groups. Clinically silent infarction may be far more frequent and could contribute to long-term cognitive dysfunction in patients after cardiac procedures. Using Diffusion-Weighted magnetic resonance Imaging we document the occurrence, vascular distribution, and procedural dependence of silent infarction after cardiac surgery with cardiopulmonary bypass. We also document the association of pre-existing white matter lesions with new postoperative ischemic lesions. **Methods.** 34 subjects underwent T2-weighted Fluid Attenuated Inversion Recovery and Diffusion-Weighted magnetic resonance imaging before and after cardiac surgery with cardiopulmonary bypass for coronary artery bypass grafting(CABG), aortic valve replacement(AVR), and mitral valve repair or replacement(MYR) surgery. Images were evaluated by experienced neuroradiologists for number, size of lesions, and vascular distribution.

**Results.** Mean age of participants was 67  $\pm$  15 years. New cerebral infarctions were evident in 6/34 subjects(18%), were often multiple, and in 67% of subjects were clinically silent. The occurrence of new infarctions by surgical procedure was as follows: AVR (2/6), CABG/AVR(3/8), AVR with root replacement(1/1), CABG/MVR (0/4), MVR (0/2), and isolated CABG(0/13). New infarction occurred in 6/15(40%) of all procedures involving aortic valve replacement. The severity of pre-existing white matter lesions trended toward predicting the occurrence of new lesions(p=.055).

Conclusion. New ischemic lesions occur in 40% of subjects after AVR.

Lesion Frequency by Vascular Region

	Herr	nisphere	
Vascular Region	Right(#)	Left(#)	
ACAa	2(11%)	l (6%)	
MCAb	l (6%)	0(0%)	
PCAc	0(0%)	l (6%)	
Watershed	7(39%)	4(22%)	
PICA4	I (6%)	4(22%)	
Totals	11/18(61%)	7/18(39%)	

### IMPACT OF CARDIAC INDEX ON CEREBRAL OXYGEN REGIONAL SATURATION

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Introduction. Compensatory mechanisms have been believed to adequately regulate cerebral blood flow in humans. It has been suggested that patients with left ventricular dysfunction and low cardiac output [LCOS] suffer from cerebral hypoperfusion. The brain is especially sensitive to circulatory changes that reduce oxygen delivery and moderate to severe cognitive impairment in patients with chronic heart failure is common. This study was designed to determine the effect of changes in cardiac index [CI] on Near-Infrared Spectroscopy [NIRS] assessment of cerebral oxygenation while other determinants of cerebral blood flow [mean arterial pressure, etco<sup>2</sup>, hematocrit, fio<sup>2</sup>, temperature] were constant.

Methods. 25 patients [mean age, 69 years male: female 17:8] undergoing general anesthesia for CABG were monitored using continuous cardiac output [CCO/SVO2] and Near-Infrared Spectroscopy [NIRS] the INVOS 4100. After baseline hemodynamics and NIRS were obtained, patients were treated with Dopamine 5 ug/kg/min. Repeat values were obtained after 15 minutes. Data presented as mean +/- S.D. Statistical analysis was performed with repeated measures ANOVA and student's t-test with p < 0.05 considered significant.

Results. Dopamine 5 ug/kg/min. significantly increased cardiac index from 1.8 +/- 0.21 to 2.8 +/- 0.45 1 / min. LrSO2% 53.9 +/- 7.7 to 70.2 +/- 7.7, and RrSO<sup>2</sup>% 52.67+/- 7.5 TO 69 +/- 9.5 [p < 0.001]. No significant changes from baseline were observed for etco<sup>2</sup>, mean arterial pressure, hematocrit, or temperature.

Conclusion. This data suggests that patients with low cardiac index despite generally normal mean arterial pressure, hematocrit, etco<sup>2</sup>, and fio<sup>2</sup> have low rso<sup>2</sup>% [cerebral oxygen delivery] and this value can be significantly improved with improving cardiac index. This data also suggests that cerebral autoregulation may well be impaired in this subset of patients and flow becomes more of a critical factor. Maintaining cardiac index and rso<sup>2</sup>% may be an important element in reducing the incidence of postoperative neurocognitive dysfunction.

### MONITORING CEREBRAL OXYGEN SATURATION IN DIABETIC PATIENTS: CLINICAL OUTCOMES

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Objective. Cerebral autoregulation and oxygenation are impaired in diabetic patients during CPB.[1,2] We determined whether preserving cerebral oxygenation (rSO2) would improve clinical outcomes in diabetic coronary artery bypass (CAB) patients.

Methods. After IRB approval and informed consent 56 diabetic patients, a subgroup of a series of 199 patients (INT,n=101; CON,n=98) undergoing CAB surgery, were randomized to intervention (INTDM,n=30) or control (CONDM,n=26) management. Bihemispheric cerebral oximetry (INVOS, Somanetics(r)) was applied in all groups and baseline saturations obtained. In the INT and INTDM groups, cerebral rSO2 was actively displayed and a protocolized series of interventions including increases in PaCO2, MAP, pump flow, FiO2, anesthesia, and Hct, were used to maintain cerebral rSO2 within 75% of baseline values. In all diabetic patients preoperative, intraoperative and postoperative glucose values and insulin administration were recorded. In the CON and CONDM groups, cerebral rSO2 signal was recorded but display was blinded. All rSO2 data was stored on computer disc for all groups for later analysis. Tepid CPB was employed using membrane oxygenator, arterial filter, alpha-stat management, and 2.0-2.5 L/M2/min nonpulsatile flow rate. A combination of anterograde and retrograde blood cardioplegia with single aortic cross clamp using LIMA and SVG was employed for revascularization. Clinical outcomes were assessed by an independent blinded clinical observer. Data were analyzed by unpaired t-test or Wilcoxon Rank Sum with p<0.05 for significance.

Results. There were no differences in perioperative glucose control, insulin administration or baseline rSO2 between either of the diabetic groups. Mean intraoperative CONDM rSO2 (60.96%), and overall rSO2 time/minutes less than 50% (143.7%min), were significantly lower than corresponding CON rSO2 values (64.5%, 53%min,  $\vec{p} = 0.034$ , p = 0.017, respectively). INTDM rSO2 was not significantly lower than INT values at any time. Vent time was 19.2 vs 11.2 hrs (p=0.377), ICU time was 66.9 vs33.9 hrs (p=0.053) and LOS was 8.1 vs 5.6 days(p=0.073) between CONDM and INTDM groups respectively, but did not differ between INT and INTDM groups.

Conclusions. Diabetic CAB patients require longer postoperative ventilation, ICU stay and postoperative length of stay than non-diabetics.[3] We demonstrated that avoidance of cerebral oyxgen desaturation in actively rSO2 monitored diabetic patients is associated with improved ICU and hospital length of stay diabetic patients undergoing CAB surgery. **References**: 1] Circulation 1990;82:407-12; 2] Anesthesiology

2000;92:1324-9; 3] Thorac Cardiovasc Surg 2003;51:11-6

### **ORGAN PROTECTION AND OUTCOMES IN 178** THORACOABDOMINAL AORTIC ANEURYSM REPAIRS IN PATIENTS WITH MARFAN SYNDROME

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Introduction. Surgical repair of extensive thoracoabdominal aortic aneurysms (TAAA) in patients with Marfan syndrome (MFS) remains challenging. The purpose of this report is to describe our experience with organ protection in patients with MFS undergoing TAAA repair.

Methods. Over a 16-year period, 178 TĂAA repairs were performed in patients with MFS. Techniques for organ protection have evolved over the study period. Strategies for spinal cord, visceral and renal protection included left heart bypass, reattachment of intercostal arteries, cerebrospinal fluid (CSF) drainage, cold renal perfusion, and selective visceral perfusion.

Results. Protection strategies and outcomes for TAAA repairs are listed (table) by extent of aortic involvement. There were 6 operative deaths (3%), 2 strokes (1%), and 15 cases (8%) of renal dysfunction/failure. There were 7 spinal cord deficits (4%). Overall survival at 5- and 10-years was 83  $\pm$  3% and 71  $\pm$  5%, respectively.

Conclusion. A multimodality approach to organ protection in MFS patients undergoing TAAA repair can contribute to successful outcomes by minimizing the threat of ischemic complications.

		Extent	of Repair	
	l (n=34)	II (n = 101)	III (n = 25)	IV (n = 18)
Protection strategy				
Left heart bypass	21 (62%)	85 (84%)	2 (8%)	0
Reattach intercostal arteries	30 (88%)	96 (95%)	18 (72%)	6 (33%)
CSF drain	12 (35%)	50 (50%)	II (44%)	ÌO Í
Cold renal perfusion	3 (9%)	46 (46%)	15 (60%)	11 (61%)
Selective visceral perfusion	I (3%)	56 (55%)	2 (8%)	Û
Outcomes	· · /	· · · ·	. ,	
Operative mortality	0	4 (4%)	2 (8%)	0
Stroke	0	L (1%)	I (4%)	0
Paraplegia or paraparesis	I (3%)	6 (6%)	Ò	0
Renal dysfunction or failure	I (3%)	13 (13%)	I (4%)	0
Bleeding requiring reoperation	1 (3%)	4 (4%)	ò	0

### THE USE OF HYPOTHERMIC CIRCULATORY ARREST (HCA) IN CABG PATIENTS WITH AN UNCLAMPABLE ATHEROSCLERÓTIC ASCENDING AORTA.

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Introduction. Cardiac surgical procedures are made significantly more complex by the presence of severe atherosclerotic disease of the ascending aorta. Applying a cross clamp to the diseased aorta can lead to significantly increased risk of death or major morbidity including stroke. Given the potential risks involved with attempts at cross clamping an ascending aorta with significant atherosclerotic burden, various strategies have been employed to manage this disease entity.

At our institution, when a severely diseased ascending aorta is encountered in a patient undergoing CABG, we employ the following strategy. The distal grafts are constructed under ventricular fibrillation while cooling systemically and the proximal vein graft anastomoses are performed under hypothermic circulatory arrest (HCA).

The purpose of this study is to compare the results of Group A, patients undergoing CABG utilizing HCA with Group B those utilizing standard techniques where the ascending aorta is cross clamped.

Methods. A retrospective review of the Cape Cod Hospital cardiac surgery database was undertaken to study patients undergoing isolated CABG beginning in August 15, 2002 through December 31, 2005. Three hundred fifty five patients underwent isolated CABG during this period, 18 of which where found to have severe atherosclerotic disease of the ascending aorta. Patients who required reoperation or those who required additional procedure(s) at the time of operation were excluded from this study. Methods to evaluate the ascending aorta in this group included: chest XR, aortic angiogram, chest CT, digital palpation of the aorta intraoperatively, and an epiaortic ultrasonic scan (EAS).

**Results.** Eighteen patients or 5.1% (Group A) were found to have severe atherosclerotic disease of the ascending aorta preventing the safe application of an aortic cross clamp. Of the 18 patients in Group A, 5 (28%) patients were women and 13 (72%) were men. In Group B, 56 patients or 16% were women. The mean age in Group A was 75.0 years compared with 68.1 years in Group B. The mortality rate for group A was 0/18 (0%) and the mortality rate for Group B was 2/337 (0.06%). There were no strokes appreciated in either group. **Discussion.** Numerous strategies have been employed to address the issue of the atherosclerotic ascending aorta. The use of hypothermic circulatory arrest (HCA) has the potential to increase morbidity and mortality. Our preliminary results indicated that the use of HCA did not significantly increase morbidity or mortality. The use of HCA appears to be a safe and reasonable approach to this difficult surgical problem. Further studies comparing HCA to other strategies may be warranted.

# OUTCOMES IN PATIENTS WITH DELAYED PARAPLEGIA FOLLOWING THORACOABDOMINAL AORTIC OPERATIONS

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**Introduction.** Limited information is available regarding treatment and outcomes of delayed paraplegia after thoracoabdominal aortic aneurysm (TAAA) repair. The objectives of this retrospective review were to assess factors that precipitate delayed-onset neurologic deficits, examine the impact of therapeutic interventions, and evaluate factors associated with favorable outcomes.

**Methods.** Over a 19-year period, 2,315 TAAA repairs were performed. Postoperative paraplegia or paraparesis developed in 92 patients (4.0%), 27 of whom (1.2%) awoke from anesthesia with intact neurologic function and subsequently developed a new spinal cord deficit. The records of these 27 patients were reviewed to determine clinical characteristics and operative details, events associated with development of the deficits, treatments employed in an attempt to reverse the deficits, and outcomes. Factors related to functional status were evaluated by comparing survivors who were ambulatory at discharge with those who were not.

**Results.** Delayed deficits occurred between 16 hours and 91 days postoperatively and were associated with a period of hypotension in 8 patients (30%). The hypotensive episodes were related to sepsis in 3 patients, atrial fibrillation in 2, acute respiratory deterioration in 2, and hemothorax in 1. Fifteen patients (56%) had paraplegia and 12 patients (44%) had paraparesis. Two patients (7%) died in hospital. Of the 25 survivors, 10 (40%) were ambulatory (3 walking independently and 7 with a walker), and 15 (60%) were nonambulatory at discharge. Factors associated with ambulation included decreasing age, male sex, and absence of chronic hypertension or diabetes. Poor functional outcomes were associated with intraoperative cerebrospinal fluid (CSF) drainage, fewer intercostal arteries reattached, postoperative CSF drain reinsertion, and administration of corticosteroids or mannitol. Actuarial survival rate at 2 years was 90  $\pm$  9% for the ambulatory patients and 40  $\pm$  13% for the nonambulatory patients (p = 0.0014).

**Conclusion.** Although precipitating episodes of hypoperfusion were common, most cases of delayed paraplegia occurred without such events; this supports the concept that other factors play an important role in the development of this complication. Outcomes were not improved by any of the therapeutic interventions implemented after the deficits occurred. Ambulatory status at discharge had a significant impact on mid-term survival.

# FROZEN ELEPHANT TRUNK TECHNIQUE FOR RADICAL SINGLE STEP TREATMENT OF AORTIC TYPE A DISSECTIONS

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**Introduction**. The frozen elephant trunk technique allows radical treatment of Type A aortic dissection, enabling a single step extensive approach of the ascending and descending aorta via the opened arch. We present our initial experience with this novel technique. **Method**. The hybridprothesis, a combined vascular prothesis with steel stents at its distal end and a proximal portion consisting of a Dacron sleeve, is placed in an antegrade fashion over the opened aortic arch during a short period of deep hypothermic circulatory arrest (mean 19min) followed by selective antegrade cerebral perfusion via a separate vascular graft anastomosed with the brachiocephalic vessels (mean 67min). This form of antegrade cerebral perfusion allows reduced duration of brain ischaemia. A preoperatively angiographically controlled transfemorally advanced guidewire facilitates correct placement of the hybridprothesis in the true lumen.

**Results.** The hybridprothesis was implanted in 7 patients diagnosed with Type A dissection (chronic dissection n=5, acute dissection n=2), mean age being  $58,8 \pm 14,5$  (range 35 to 75). All patients survived the operative procedure, one patient died within the thirty day follow-up period due to multiorgan failure caused by biventricular heart failure. Psychoorganic syndrome occurred in one patient, there was no stroke or paraparesis.

**Conclusion**. The novel operative procedure using the frozen elephant trunk technique allows an extensive one-stage approach for the treatment of type A dissection with closure of multiple entries/re-entries in the descending aorta.

### SELECTIVE ANTEGRADE CEREBRAL PERFUSION WITH AXILLARY ARTERY CANNULATION ATTENUATES CEREBRAL INJURY IN AORTIC ARCH SURGERY

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**Introduction**. Aortic arch surgery has a high incidence of brain injury. We hypothesized that selective antegrade cerebral perfusion(SACP) associated with right axillary artery cannulation would reduce neurological injury.

Methods. In a retrospective non randomized study, between January and July 2005,41 adult patients were underwent to either HCA(11) or SACPHCA occurred at a nasopharyngeal temperature of 15°C and SACP at a corporeal temperature of 26°C with cerebral perfusion at 15°C.In 19 patients the systemic perfusion as been obtained by femoral cannulation, in 22 patients the right axillary artery as been cannulated; in the latters the cerebral perfusion as been obtained cannulation either the common left carotid artery or the left subclavian artery.Axillary artery cannulation was successful in all patients; it provided sufficient arterial flow and there were no intraoperative problems with perfusion.Continuous transcranial Doppler monitoring of middle cerebral artery velocity(MCAV) was performed.

**Results.** There were I hospital death in group with HCA(2,4%). There were 23% of neurological complications in group with HCA and 12% in the group with SACP with a p value of 0,04. Also the bleeding complications were significantly lower in SACP group.

**Conclusion**. SACP attenuates the neurological damage in aortic arch surgery. In the presence of severe thoracic aorta disease, arterial perfusion through the axillary artery is a safe and effective means of providing sufficient arterial inflow during cardiopulmonary bypass. In this regard, it is an excellent alternative to standard femoral artery cannulation. Further studies are required to assess optimal perfusion conditions and clinical outcome.

# A GENETIC BASIS FOR COGNITIVE DECLINE AFTER CARDIAC SURGERY

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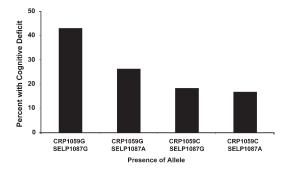
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**Introduction.** Cognitive decline is a common complication of CABG surgery and is associated with a reduced quality of life. Since many studies suggest that genetic factors account for over 50% of the variance in adult cognitive abilities, we hypothesized that candidate gene polymorphisms in biological pathways regulating inflammation, cell matrix adhesion/interaction, coagulation-thrombosis, lipid metabolism and vascular reactivity are associated with postoperative cognitive dysfunction.

Methods. In a prospective cohort study of 677 patients undergoing CABG surgery with cardiopulmonary bypass, a panel of 37 SNPs was genotyped by Matrix Assisted Laser Desorption/Ionization Time-Of-Flight mass spectrometry. Association between these SNPs and cognitive deficit at 6-weeks after surgery was tested using multiple logistic regression accounting for age, level of education, baseline cognition, and population structure. Permutation analysis was used to account for multiple testing.

ysis was used to account for multiple testing. **Results**. We found that minor alleles of the *CRP* 1059G/C SNP (OR: 0.37, 95% Cl: 0.16-0.78, p = 0.013) and the *SELP* (P-selectin) 1087G/A SNP (OR: 0.51, 95% Cl: 0.30-0.85, p = 0.011) were associated with a reduction in cognitive deficit. The absolute risk reduction in the observed incidence of POCD was 20.6% for carriers of the *CRP* 1059C allele and 15.2% for carriers of the *SELP* 1087A allele. Serum CRP and degree of platelet activation were also significantly lower in patients with a copy of the minor alleles, providing biological support for the observed allelic association.

**Conclusion**. We report a genetic basis for the cognitive decline commonly seen after cardiac surgery. A diminution of the perioperative inflammatory and prothrombotic state may be beneficial in reducing this deficit.



# COMPREHENSIVE CEREBRAL PROTECTION DURING OPERATIONS INVOLVING THE AORTIC ARCH

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**Introduction.** Successful aortic arch operations provide comprehensive cerebral protection (CCP) and effective surgical correction. CCP must prevent cerebral embolism (CE) at the onset and conclusion of the pump run and it must minimize intraoperative cerebral ischemia. We have developed a technique that achieves these ends and simplifies most aortic arch operations. Our approach utilizes 3 concepts: (1) separate arterial cannulation of the cerebral (innominate or carotid) and systemic (distal arch or femoral) circulation, (2) separate heat exchangers for each circulation, (3) clamp separate of the voc circulations.

Methods. Using these strategies, we operated upon 71 consecutive, unselected patients from Jan 2002 - Dec 2005: 19 Type A dissections, 22 arch aneurysms, and 30 patients with mobile arch atherosclerosis and/or aortic calcification (GrIV/Ca<sup>++</sup>) too severe to permit clamping. In all cases, we used transesophageal echocardiography, we applied a clamp to the cannulated head vessel, and began cerebral perfusion at 1 L/min before starting the systemic bypass. This effectively isolates the cerebral circulation from embolism at the onset of cardiopulmonary bypass. At the end of the operation, we discontinued systemic bypass before unclamping and discontinuing the cerebral perfusion. This reduces the chance for CE at the end of the operation. When we cooled the brain, we never actively re-warmed beyond 32-33°C. For the dissections, we cooled the brain to 20°C and the body to 30°C, and performed the distal aortic anastomosis first using systemic arrest. Differential cooling substantially reduces re-warming time. We then clamped the graft and re-warmed the body while completing the operation. For the other cases, we varied cannulation technique and cooling to fit the problem always following the rules stated above. The majority of those with GrIV/Ca<sup>+</sup> required AVR, CABG, or both. We never resected Grade IV aortas unless they were part of an aneurysm. We simply corrected the indicated pathology and prevented CE.

#### Results. See Table.

**Conclusions.** Among these patients, none died of cerebral complications, and only one suffered a stroke. CCP provided excellent cerebral protection and reasonable outcomes in these high-risk aortic arch cases.

Factor	Dissection $(n=19)$	Arch Aneurysm (n=22)	GrIV/Ca++(n=30)
Perioperative Stroke	5.3% (1)	0% (0)	0% (0)
Operative Mortality	5.3% (I)	4.5% (I)	16.7% (5)
Median Postop LOS	10.0 days	9.0 days	9.5 days

# A BRIEF VERSION OF THE CES-D AS A SCREEN FOR DEPRESSIVE SYMPTOMS BEFORE CARDIAC SURGERY

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Introduction. The CES-D has been used extensively in cardiac surgical patients to measure depression. A relationship between CES-D score and

**Methods.** Of the 20 CES-D items, we attempted to find the top five predictor items, and examine the performance of predictor subsets composed of these items. There were 1922 CES-D questionnaires that were completed by study participants at baseline, 1, 3, 12, and 36 months. All patients provided written informed consent. The data were separated into a training set and validation set. Using different 2 and 3 item subsets of the top five CES-D items, we fit a model of CES-D score on a predictor subset using the training data. These models allowed for two-way item interactions. We then used the estimates of the model coefficients to predict CES-D scores in the validation data set.

**Results**. The top five items in the single predictor model are items: F, C, R, L, and P (see table for each item statement). Using two items combined, F & L were the most predictive; with three items combined, F, R, & L were the most predictive. **Conclusion.** A brief form of the CES-D that may accurately predict the entire 20 question CES-D score has been developed. If a pilot study in a new population of patients supports the initial finding, this shortened form could be used in medical settings to more rapidly identify those patients in need of further evaluation for depression.

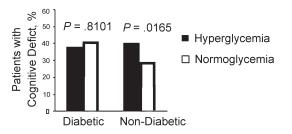
ltem	CES-D item statement	% Variability explained
F	l felt depressed	60%
C	I felt that I could not shake off the blues, even with the help from my friends	53%
R	I felt sad	52%
L	l was happy	46%
Р	l enjoyed life	46%

# HYPERGLYCEMIA AND INCREASED INCIDENCE OF COGNITIVE DEFICIT AFTER CARDIAC SURGERY

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**Introduction.** Hyperglycemia, which is known to exacerbate other forms of cerebral injury, has been incompletely studied in the setting of post-cardiac surgery cognitive loss. We hypothesized that intraoperative hyperglycemia would increase the risk of cognitive deficit in patients undergoing coronary artery bypass graft (CABG) surgery. **Methods.** Following IRB approval, we identified on-pump CABG patients

who had participated in non-interventional studies examining postoperative cognitive loss. Cognitive testing was performed both preoperatively (baseline) and 6 weeks after surgery. A cognitive deficit was defined as a standard deviation decline in at least one of four cognitive domains identified using factor analysis. Hyperglycemia was defined as an intraoperative glucose ≥ 200 mg/dl. Chi-square testing and multivariable logistic regression (controlling for age, years of education, and baseline cognitive function) were used to determine the relationship between hyperglycemia and cognitive deficit. Results. In the 525 patients included in this analysis, hyperglycemia occurred in 393 (75%) patients with a peak glucose of  $237 \pm 58 \text{ mg/dl}$ . In the non-diabetic patients (n = 380), even after controlling for age, years of education and baseline cognitive function, the incidence of cognitive deficit was significantly higher in patients experiencing hyperglycemia (40% hyperglycemia vs. 29% normoglycemia; OR, 1.85, 95% Cl 1.12-3.04;p=0.0165). However, hyperglycemia had no effect on the incidence of cognitive deficit in the diabetic patients (38% hyperglycemia vs. 41% normoglycemia; OR 0.89, 95% CI 0.35-2.27; p=0.8101). Conclusion. In non-diabetic patients, hyperglycemia is an independent risk factor for postoperative cognitive deficit, increasing the odds of developing cognitive deficit by as much as 85%.



# QUANTIFYING COGNITIVE CHANGE AFTER CABG: DECLINE OR NORMAL VARIABILITY?

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**Introduction.** Attempts to quantify cognitive change after CABG have led to highly variable results. Many studies did not utilize control groups, so that decline must be based on an arbitrary measure of change within the study population. Notably, any estimates of the incidence of decline are uninterpretable unless reference is made to a control group.

**Methods.** We used an existing cognitive data set of 110 CABG, 85 non-surgical cardiac controls, and 64 heart healthy controls and applied an arbitrary criterion of 20% decline on one or more tests to simulate results. Cognitive scores were compared from 3 to 12-month follow-up.

**Results.** The results clearly demonstrate that there is considerable variability (both improvement and decline) in the follow-up performance of all groups. The table below shows the percentage of patients who declined or improved by more than 20% on at least 1, 2, 3, or 4 (of a total of 16) cognitive measures.

**Conclusion.** This simulation demonstrates that the commonly used definition of 20% decline will substantially overestimate the number of subjects who will be classified as having decline. If within-subject changes in cognitive test performance are used as outcomes, it is critical to include appropriate control groups, as well as expressing both decline and improvement in test performance.

# Tests		Declined			Improved	
	CABG	NSCC	HHC	CABG	ŃSCC	HHC
1	77%	84%	59%	89%	91%	86%
2	53%	49%	38%	67%	74%	67%
3	31%	28%	16%	55%	46%	39%
4	15%	11%	5%	32%	27%	23%

# AGING & IMPAIRMENT OF WORKING MEMORY WITH ACUTE ISOVOLEMIC ANEMIA

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**Introduction.** Aging is the greatest risk factor for cognitive dysfunction after cardiac and noncardiac surgery. Cardiac, major vascular, and orthopedic surgery, are often associated with significant blood loss and a rather acute state of isovolemic anemia. Acute isovolemic anemia has been found to cause acute cognitive decline even in healthy subjects. We hypothesize that acute anemia may have an important role in postoperative cognitive dysfunction after major surgery across the various disciplines.

**Methods.** Working memory was studied in two groups of young(3 months of age) Spontaneously Hypertensive rat(SHR), sham(YS-S) and test(YS-T) animals, and two groups of aged(18 months of age) SHR, sham(AS-S) and test(AS-T) animals following the creation of a state of isovolemic anemia. Following a 2 week water maze training period, rats underwent a hemodilution protocol. Animals were allowed a 24 hour recovery period prior to water maze testing. Beginning on post-hemodilution day #2, animals were challenged with a working memory platform paradigm for 10 consecutive days, with 10 possible platform locations for each day. Trial length was lim-

ited to 90 seconds, with 8 trials per day the maximum allowed. If the rat did not find the platform within 90 seconds, it was guided to the platform and was allowed to stay there for 10 seconds. To be allowed to move to the next platform location on the next day, rats had to reach the criteria of finding the platform within 15 seconds for three consecutive trials. Otherwise, the rat was challenged with the same platform location on the following day. When each rat reached criteria, trials ceased for that day and that platform location. The number of trials to reach criteria was recorded.

**Results.** Aged SHR(AS-T) demonstrated a significant working memory impairment that was not seen in any of the younger(YS-S or YS-T) or aged(AS-S) groups, as evidenced by the increased number of trials required to reach platform criteria.

**Conclusion.** Acute anemia impairs working memory in an age dependent manner. Acute anemia may account for cognitive dysfunction across surgical disciplines.

Group	N	TRIALS	P=
YS-S	7	4.6 ± 1.6	<.05
YS-T	7	4.9 ± 1.5	<.05
AS-S	8	5.4 ± 2.0	<.05
AS-T	15	7.8 ± 4.1	

### HYBRID ROBOTIC CORONARY ARTERY BYPASS GRAFTING AND PERCUTANEOUS CORONARY INTERVENTION FOR MULTIVESSEL DISEASE

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London Health Sciences Centre, University Hospita, I London, Ontario, Canada **Background**. In the past decade, two-stage hybrid coronary artery revascularization, a combination of coronary artery bypass grafting through minithoracotomy and percutaneous coronary intervention (PCI), has been described. We report our experience with one-stage hybrid robotic-assisted coronary artery bypass grafting and PCI.

**Methods.** 35 patients underwent concurrent hybrid coronary artery revascularization at our institution. 31 were males; mean age was 61 years (44-82 years). All internal thoracic arteries were harvested with robotic-assistance, and all anastomoses were manually constructed through a mini-thoracotomy without cardiopulmonary bypass. Subsequently, in the same operating room, graft patency was confirmed and PCI was carried out using drug-eluting stents. In 22 patients bivalirudin was utilized during the entire procedure.

**Results.** There were no mortalities, no wound infections, and one perioperative myocardial infarction. Length of stay in the intensive care unit averaged I day and median length of hospital stay was 4 days. Three patients required post-operative exploration for bleeding. One patient had a stroke. All patients were free of symptoms at 20 months follow-up. At 6 months angiographic follow-up, twelve patients had patent anastomosis and stent.

**Conclusions.** Concurrent robotic-assisted hybrid coronary artery revascularization is safe and feasible. This approach allows complete multivessel revascularization with decreased surgical trauma and post-operative morbidity. Further results are necessary to determine patient selection and long term benefits.