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2006;102,SCA1-97

SCA30

A SELECTIVE INHIBITOR OF APOPTOTIC PROTEIN P53 ENHANCES ISOFLURANE-INDUCED CARDIOPROTECTION DURING EARLY REPERFUSION IN RABBITS

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Introduction: Brief exposure to isoflurane before and during early reperfusion after coronary artery occlusion protects against myocardial infarction by activating phosphatidylinositol-3-kinase (PI3K)-mediated signal transduction(1). The apoptotic protein p53 is regulated by PI3K, and inhibition of p53 has been previously shown to protect against ischemic injury in isolated rat hearts(2). Whether p53 mediates isoflurane-induced postconditioning is unknown. We tested the hypothesis that inhibition of p53 enhances protection against infarction produced by isoflurane during early reperfusion.
Methods: Barbiturate-anesthetized rabbits (n=36) were instrumented for the measurement of systemic hemodynamics and subjected to a 30 min left anterior descending coronary artery occlusion followed by 3 h reperfusion. In six experimental groups, rabbits were randomly assigned to receive 0.9% saline (control), isoflurane [0.5 or 1.0 minimum alveolar concentration (MAC)] administered for 3 min before and 2 min after reperfusion, the selective p53 inhibitor pifithrin alpha (PIF; 1.5 or 3.0 mg/kg) dissolved in dimethylsulfoxide and administered intraperitoneal 30 min before coronary occlusion, or 0.5 MAC isoflurane plus 1.5 mg/kg PIF. Myocardial infarct size was determined using triphenyltetrazolium chloride staining. Statistical analysis was performed with ANOVA followed by the Student-Newman-Keuls test (*$P<0.05$). Data are mean±SD.
Results: Systemic hemodynamics and left ventricular area at risk were similar between groups. Isoflurane (1.0 but not 0.5 MAC) and PIF (3.0 but not 1.5 mg/kg) reduced ($P<0.05$) infarct size [21±4*, 43±7, 22±6*, and 43±7%, respectively, of left ventricular area at risk] as compared to control (44±4%). Isoflurane (0.5 MAC) plus 1.5 mg/kg PIF also produced protection (28±3*%).
Conclusions: The results of the current investigation indicate that inhibition of the apoptotic protein p53 enhances isoflurane-induced cardioprotection during early reperfusion in vivo.
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SCA31

WORSENING OF LONG-TERM MYOCARDIAL FUNCTION AFTER SUCCESSFUL PHARMACOLOGICAL PRECONDITIONING WITH CYCLOSPORINE

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Preconditioning with cyclosporine (CsA) has been shown to decrease infarct size 24 hours after myocardial ischemia/reperfusion (I/R) injury. The goal of this study was to determine the effects of CsA preconditioning on long-term outcome and cardiac function after I/R-injury. Male Sprague-Dawley rats were randomly assigned to three treatment groups: 1) vehicle only, 2) CsA, 5mg/kg/day, and 3) CsA, 12.5mg/kg/day. Treatment was given via oral gavage for three days prior to I/R-injury (30 minutes of left anterior descending [LAD] coronary artery occlusion). We evaluated post-I/R survival and cardiac function by transthoracic echocardiography and invasive left ventricular hemodynamic measurements 14 days after I/R-injury. Rats with I/R-injury showed an overall increased left ventricular end diastolic pressure compared to rats without I/R-injury ($p<0.005$). Although CsA initially decreased infarct size, no differences of left ventricular end diastolic pressure (LVEDP) were seen 14 days after I/R-injury (vehicle: 21.2±8.9 mmHg, CsA 5 mg/kg/day: 21.5±0.7 mmHg, CsA 12.5 mg/kg/day: 20.5±9.4 mmHg). Ejection fraction and fractional shortening were decreased in all groups compared to baseline, but no differences between groups were observed. On day 14, a dose-dependent increase in left ventricular end diastolic diameter was seen ($p<0.001$). CsA pretreatment was also associated with a dose-dependent decrease in post-I/R survival (vehicle: 56%, CsA 5mg/kg/day: 32%, CsA 12.5mg/kg/day: 16%; $p=0.017$). CsA preconditioning did not improve long-term cardiac function despite decreased infarct size 24 hours after I/R-injury, and increased post-I/R mortality significantly. Poor cardiac function after CsA preconditioning seems to be related to dose-dependent left ventricular dilation.

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SCA32

CLINICAL, PROCEDURAL AND GENETIC DETERMINANTS OF QTC PROLONGATION FOLLOWING CARDIAC SURGERY

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Introduction: Prolongation of corrected QT (QTc) interval has been associated with risk of cardiovascular adverse events in a broad range of clinical populations,1 including patients undergoing non-cardiac surgery.2 Although long-term changes in ventricular repolarization following coronary revascularization have been reported,3,4 the impact of cardiac surgical injury on early postoperative repolarization abnormalities is not known. We tested the hypothesis that clinical, procedural and genetic factors are associated with perioperative changes in QTc interval in cardiac surgical patients.

Methods: After excluding patients with ventricular conduction abnormalities (bundle branch blocks), pacemaker, perioperative atrial fibrillation, or receiving perioperative antiarrhythmic drugs in the study period, 460 patients who underwent cardiac surgery (CABG, valve, or combined CABG/valve) using cardiopulmonary bypass were selected. QTc intervals were measured from 24-hour pre and postoperative 12-lead ECG by two investigators blinded to genetic data; prolonged QTc was defined as >440 msec. Number of intraoperative cardioversions upon aortic cross-clamp release was recorded as an index of reperfusion arrhytmias.5 MALDI-TOF mass spectrometry was used to genotype 45 single-nucleotide polymorphisms (SNPs) in 24 candidate genes modulating pathways implicated in arrhythmia susceptibility. A multivariate regression model including demographic and procedural covariates was developed. A two-step strategy 6 was used for genetic analyses – marker selection, followed by clinico-genomic model building. Bonferroni correction was used to adjust for multiple comparisons.

Results: QTc interval was significantly prolonged following cardiac surgery with cardiopulmonary bypass ($p<0.01$), and was associated with higher incidence of intraoperative reperfusion arrhythmias ($p=0.006$). Gender, age, procedure and cross-clamp time were independent predictors of QTc prolongation. Moreover, two functionally important SNPs in [SPCHAR(beta)]2 adrenergic receptor (ADRB2) and interleukin-1[SPCHAR(beta)](IL1B) genes were independently associated with postoperative QTc prolongation.

Conclusions: Perioperative QTc is modestly but significantly prolonged following cardiac surgery. This may reflect disrupted electrophysiological stability of the myocardium and thus substrate for triggering malignant arrhythmias. Two functional variants in genes related to inflammation and adrenergic responsiveness are independent risk factors for postoperative QTc prolongation. This may aid in perioperative identification and monitoring of high-risk cardiac patients and the development of novel cardioprotective strategies.

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Table: Combined clinical-genetic multivariable models for postoperative QTc prolongation in cardiac surgical patients

	Preop	Postop
QTc* (msec)	402±29	421±32
Incidence of Prolonged QTc (%)	9.30	22.3
Clinical model (r^2=0.39)	**F-value**	**p-value**
QTc-preop	175.51	<0.0001
Gender	7.45	0.006
Age (y)	7.76	0.006
Procedure	3.78	0.011
Cross-clamp time (min)	5.27	0.023
Race (self-reported)	0.40	0.669
Clinico-genomic model (r^2=0.45)		
IL1B(rs16944)/*ADRB2*(rs1800888)	5.68	0.044#

* Bazett's formula

\# Bonferroni-adjusted p-value

SCA33

IMMEDIATE EXTUBATION: A ROUTINE AFTER OPEN-HEART SURGERY? A PROSPECTIVE STUDY OF 635 PATIENTS.

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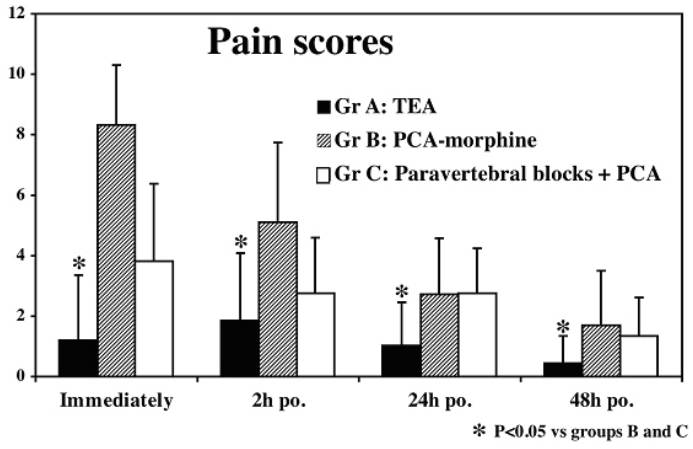
Objective: The purpose of this study is to examine the feasibility of routine immediate operating room extubation (ultra-fast-track-anaesthesia-UFT) during open-heart surgery and to focus on pain scores comparing various anesthetic and analgesic techniques.
Methods: 635 consecutives patients undergoing cardiac surgery with an ejection fraction (EF) of at least 25 % were included in this prospective audit. Patients received different regimens of analgesia: group A) high T2/T3 thoracic epidural analgesia (TEA) installed preoperatively and removed after 72 h; B) fentanyl during surgery and postoperative patient-controlled analgesia (PCA)-morphine; or C) bilateral paravertebral blocks + fentanyl followed by PCA-morphine. Anesthesia was induced using standard protocols with fentanyl and propofol, and maintained using sevoflurane titrated to a Bispectral index (BIS) monitoring of 40-50. All patient data were recorded; pain scores were compared between groups using Kruskal Wallis test, $P < 0.05$.
Results: Mean age was 63 ± 11 years (range: 27-91), weight 77 ± 16 kg (43-140), 12% have EF <40%, 59% high blood pressure, 14% COPD, and 25% diabetes. 461 patients underwent off-pump CABG, 29 on-pump CABG, 110 aortic valve replacements simple or combined, 35 mitral valve replacements or reconstructions. Duration of surgery was 123 ± 31 min (35-295), ischemic time during aortic cross clamp 44 ± 16 min (13-103). All patients were successfully immediately extubated after cardiac surgery in the operating room within 15 ± 5 minutes, no differences between groups, and sent to postoperative anesthesia care unit for 2-4 hrs for stabilisation. Post-operative pain scores were significantly lower in the TEA group, see figure. There was no complication related to epidural catheter placement and no neurologic complications. Only three patients needed re-intubation, two due to respiratory failure within 60 minutes after extubation and one secondary to myocardial infarction (MI). Perioperative mortality was 1%, MI and low output syndrome occurred in 2.4% and 2.7% respectively, 17% needed blood transfusion, and atrial fibrillation was noticed in 17%.
Conclusion: Our study proved the feasibility and security of immediate extubation after coronary surgery, but also with heart valve surgery using cardiopulmonary bypass. Significantly better postoperative pain scores were achieved with TEA. UFT allows fast rehabilitation, and may help lowering the costs of health care.



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SCA34

ISOFLURANE ATTENUATES APOPTOSIS AFTER REGIONAL MYOCARDIAL ISCHEMIA AND REPERFUSION IN RABBITS VIA PHOSPHATIDYLINOSITOL-3-KINASE/AKT SIGNALING

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Objectives: The present study was designed to test whether anesthetic preconditioning attenuates myocardial apoptosis and whether the phosphatidylinositol-3-phosphate (PI3K)/Akt pathway is involved in regulation of anesthetic induced cardioprotection.

Methods: Using a model of regional myocardial ischemia and reperfusion, rabbits were subjected to 40 minutes of ischemia followed by 180 minutes of reperfusion and were assigned to the following groups: a control group of ischemia and reperfusion (I/R), anesthetic (1 minimal alveolar concentration of the anesthetic isoflurane) preconditioning group and a group that was exposed to combination of isoflurane and the PI3K inhibitor, wortmannin (0.6 mg/kg intravenously). A sham-operated, wortmannin + I/R and wortmannin + sham groups were also included. Myocardial infarct size was assessed by 2,3,5-triphenyltetrazolium chloride staining. Myocardial apoptosis was evaluated by terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) and activated caspase 3 assays. Phosphorylation of Akt, a downstream target of PI3K was assessed by Western blotting.

Results: Isoflurane reduced infarct size compared to the control group: 22±4% vs. 41±5% ($p<0.05$). The percentage of apoptotic cells decreased in the isoflurane group (3.8 ± 1.2%) compared to control group (12.4 ± 1.6%; $P < 0.05$). These results were also confirmed by the activated caspase-3 assay. Wortmannin inhibited the effect of isoflurane: myocardial infarction increased to 44 ± 3% and the percentage of apoptotic cells was 11.9 ± 2.1%. Akt phosphorylation increased after isoflurane preconditioning. Wortmannin blocked this effect as well.

Conclusion: Isoflurane protects the heart against ischemia and reperfusion by decreasing apoptosis and subsequently infarct size via activation of PI3K.

SCA35
OUTCOMES OF PREDICTING MITRAL SYSTOLIC ANTERIOR MOTION (SAM) IN MITRAL VALVE REPAIR

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The occurrence of SAM after CPB in patients undergoing mitral valve repair (MVP) can add significant morbidity to a hospital course. Predicting SAM based on preCPB TEE findings allows the surgeon to take preventive measures during initial repair such as upsizing the annuloplasty ring and placing an edge to edge suture (E2E) between mitral leaflets(usually A2 to P2)(Fig 2). Making predictions of SAM has not been common practice, however, because TEE predictive criteria have not been validated. The Maslow and Levine study, which is most cited on this topic, analyzed only 11 patients with SAM(1).
With IRB approval, we studied intraop (BWH Anes TEE Database) and post-discharge outcomes in 1,612 patients undergoing MVP from 1999 to 2003. Of these, 347 had documented TEE assessment of SAM postop (Group 1). When preCPB prediction of SAM was performed, predictive criteria were multifactorial and varied by anesthesiologist. Criteria were the Maslow Criteria [coaptation to ventricular septum (C-sept.) and mitral annulus distances], symmetry of anterior leaflet lengths, subvalvular attachment location of chordae, degree of mitral override of ventricular septum (aortic-mitral angle), and presence of SAM on LV unloading during initiation of CPB.
In 20 patients (Group 2), E2E was performed based on predicted SAM. In Group 2, incidence of post-CPB SAM was 0%.
Overall incidence of SAM in Group 1 was (54/347) 15.2%. SeriousSAM (re-operation [n=7] or prolonged hemodynamic management [n=15]) was 6.3%. Comparison of Group 1 vs Group 2 SAM incidence by one-tailed Fisher's Exact test was significantly different (p=0.037). Comparing e2e [0/20] with serious SAM [22/347] trended toward significance, but p=0.302.
Figure 2 shows the mitral valve from the LV apex with an E2E suture in place, and demonstrates that mitral orifice size is very adequate with E2E. Figure 1 shows postop mitral inflow after E2E; inflow is not sig. impaired.
No patient of the 20 with E2E in this series had mitral stenosis or mitral regurgitation on follow-up transthoracic ultrasound from 1-3 years post operatively.

Predicting SAM is presently a clinical judgment based on multiple TEE findings. The predictive impact of individual findings will require further quantitation and analysis of our datasets. However, the present data shows that clinical prediction of SAM and resulting preventive action by surgeons can significantly reduce the incidence of post CPB SAM without long-term adverse impact on valvular function. Examination of our entire cohort, now over 1,800 MVP patients, should allow validation of TEE predictors of SAM.

References:
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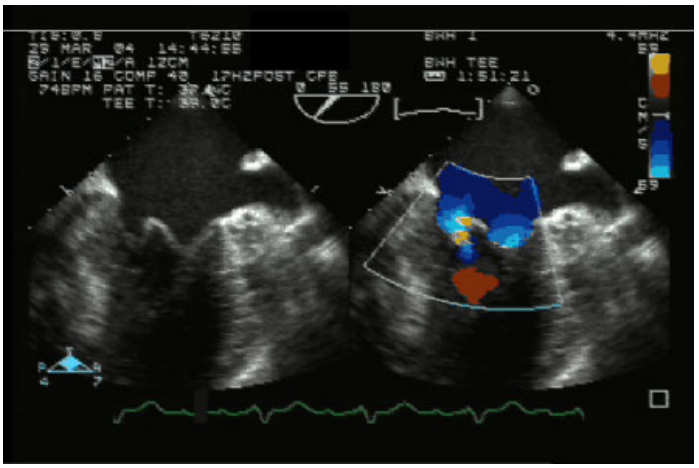

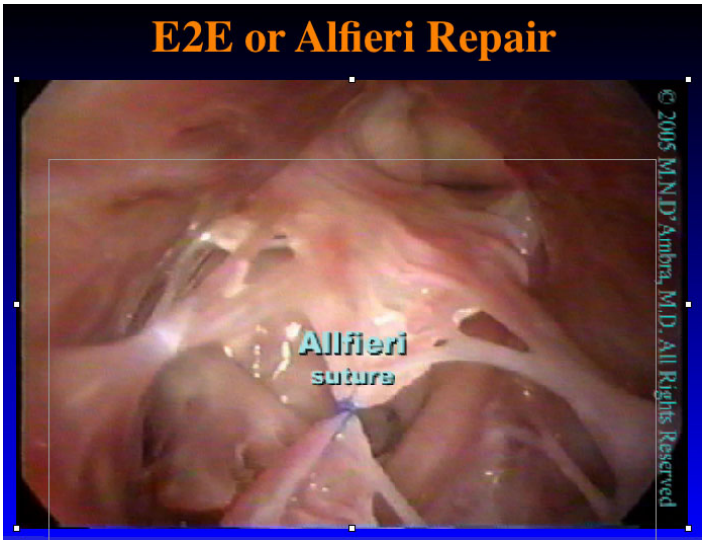

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SCA36

SEVERE DECREASES IN ANTITHROMBIN III ACTIVITY: SHOULD WE BE MONITORING THEM DURING DEEP HYPOTHERMIC CIRCULATORY ARREST?

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Introduction: Antithrombin III (AT) is the body's most effective regulator of coagulation. Levels of AT activity decrease to approximately 50% during routine cardiopulmonary bypass (CPB).1 Cases of catastrophic thrombosis associated with this acquired AT deficiency have been reported.2 Deep hypothermic circulatory arrest (DHCA), with its prolonged CPB times, hypothermia, and blood stasis, would be expected to place an even further stress on regulation of coagulation. In this pilot study, we wanted to investigate the effects of DHCA on AT activity levels.

Methods: We collected AT levels on adult patients undergoing elective cardiac procedures with DHCA. Heparin (400 units/kg) was given prior to onset of CPB, with additional doses given to keep the kaolin activated clotting times greater than 480 seconds. Circulatory arrest was carried out at a nasopharyngeal temperature of 18°C. Full dose aprotinin was used (2 million KIU load, 500,000 KIU per hour infusion, 2 million KIU placed in CPB prime volume). At the end of the procedure, heparin was reversed with 3-4 mg/kg of protamine. AT activity levels were obtained prior to systemic heparinization and after termination of CPB, before any protamine or blood products were given.

Results: The mean CPB time was 200±15 minutes. The mean DHCA time was 24±4 minutes. Baseline and post-CPB AT activity levels for each patient are shown in figure 1. The mean baseline value was 85±4% and mean post-CPB value was 37±4%. No thromboembolic complications occurred in any patient.

Discussion: Although limited by a small sample size, our study shows that AT levels fall after DHCA by a magnitude somewhat greater than that previously reported. During DHCA, this low level of AT activity may be finely balanced by decreased plasma factors and platelet counts. Case reports have described catastrophic thrombosis after DHCA following protamine or platelet administration.3,4 Although AT levels were not reported with these cases, one could hypothesize that they became too low to regulate the normal coagulation process. Further research into this area is needed to determine if AT activity should be monitored and increased in patients undergoing DHCA.

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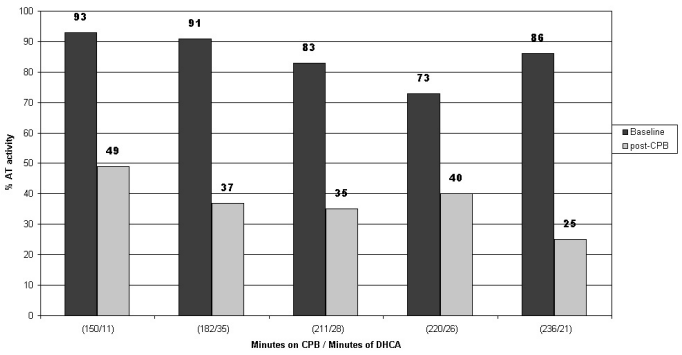
Figure 1: Changes in AT activity level



SCA37

IMPROVED CLOT FORMATION BY COMBINED ADMINISTRATION OF FIBRINOGEN AND ACTIVATED FACTOR VIIA

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Introduction: Case reports have suggested that recombinant activated factor VII (rFVIIa) is effective for refractory bleeding after cardiopulmonary bypass (CPB). However, its indication in non-hemophilic patients has not clearly been established, and there is no standardized protocol for administering rFVIIa with other hemostatic components. Because of the pivotal role of fibrinogen in clot formation, we investigated the in vitro hemostatic effects of rFVIIa and fibrinogen concentrate using RoTEM[SPCHAR(reg)] Haemostasis Analyser.
Method: After IRB approval and informed consent, blood samples were obtained from 7 healthy volunteers and 7 cardiac surgical patients following CPB. rFVIIa (NovoNordisk, Princeton, NJ), fibrinogen concentrate (Aventis-Behring, Marburg, Germany), and Ro-TEM® (Pentapharm, Munich, Germany) were used in the study. In the preliminary experiment, coagulopathy was simulated by in vitro addition of heparin (0.1 U/ml) to platelet poor plasma. Using heparinized plasma and post-CPB whole blood samples, RoTEM[SPCHAR(reg)] was performed according to manufacturer's instructions in recalcified samples with kaolin activation. We obtained three variables; clotting time (CT sec), angle ([SPCHAR(deg)]) and maximal clot firmness (MCF mm) in control (no treatment) and in vitro treatment samples. The treatment included fibrinogen (final concentration 100 mg/dl), rFVIIa (1.5 [SPCHAR(micro)]g/ml), and fibrinogen(100 mg/dl) plus rFVIIa (1.5 [SPCHAR(micro)]g/ml). Data are shown in mean[SPCHAR(plusmn)]SE. Paired t-test was used for comparison, and P<0.05 was considered significant.
Results: Table 1 summarizes the preliminary RoTEM® experiments in samples treated with heparin, and samples with heparin plus hemostatic agent. Heparin addition prolonged the onset of clotting. Addition of fibrinogen increased the amplitude (Fig, double arrow) whereas rFVIIa shortened the clotting time (Fig, arrow). In clinical samples, hematocrit and platelet count were 26[SPCHAR(plusmn)]1.2 and 45[SPCHAR(plusmn)]7.0 after protamine administration. Table 2 includes RoTEM variables for native and hemostatic agent-treated samples. Similar to findings in volunteer samples, we observed the most prominent improvement of clotting in co-administration of rFVIIa and fibrinogen.
Conclusion: The hemostatic effect of rVIIa is reflected in shorter onset of clotting, whereas fibrinogen improves the clot strength. Treatment of clinical post-CPB bleeding should include initial step of normalizing fibrinogen levels with cryoprecipitate (or fibrinogen concentrate in Europe) in order to optimize the response to rVIIa.

Reference:
J Thrombosis Haemostasis 2004;2:102-110

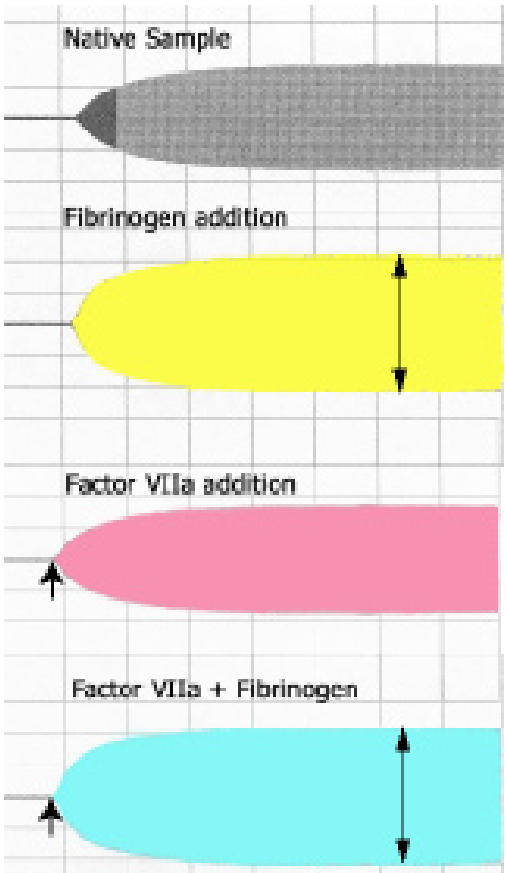
Table 1

Heparinized PPP	CT (sec)	Angle (°)	MCF (mm)
Control	615 +/- 35.3	55.3 +/- 1.8	25.0 +/- 0.5
Fibrinogen	535 +/- 31.3	62.1 +/- 1.9	29.1 +/- 0.5*
rFVIIa	452 +/- 24.9*	62.3 +/- 1.3	25.3 +/- 0.5
Fibrinogen+FVIIa	340 +/- 22.0*	68.2 +/- 1.3*	28.9 +/- 0.4*

Table 2

Post-CPB WB	CT (sec)	Angle (°)	MCF (mm)
Control	719 +/- 48.2	43.2 +/- 2.9	32.3 +/- 2.2
Fibrinogen	633 +/- 40.1	53.7 +/- 2.2*	43.1 +/- 1.5*
rFVIIa	558 +/- 79.8*	42.1 +/- 6.0	31.2 +/- 4.5
Fibrinogen+FVIIa	508 +/- 36.8*	52.1 +/- 2.4*	42.4 +/- 1.3*

PPP=platelet poor plasma, WB=whole blood, CT=clotting time, MCF=maximal clot firmness
*P<0.05 vs. control



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SCA38

IS THE ROUTINE USE OF CERTIFIED REGISTERD NURSE ANESTHETISTS ASSOCIATED WITH A HOSPITAL'S RISK-ADJUSTED CABG SURGERY SURVIVAL RATES?

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Purpose: There is substantial debate among clinicians concerning the appropriate role of certified registered nurse anesthetists (CRNAs) in complex cardiac surgery cases. Because off-pump coronary artery bypass graft (OPCAB) surgery often requires an intensive anesthetic experience, this abstract attempts to compare hospital average risk-adjusted survival rates between hospitals that routinely use CRNAs for OPCAB versus those hospitals that do not.

Method: The primary data source, HCA Heart Services Standards Database (HSSD), is a web-based survey containing detailed information regarding structures and processes in place at each of 158 HCA hospitals. The study population includes 54 HCA hospitals that performed OPCAB surgery on at least 10 patients during 2004. Hospitals were divided into two groups: hospitals that routinely use CRNAs for OPCAB surgery and hospitals that do not routinely use CRNAs during these cases. A risk-adjusted CABG surgery mortality model, controlling for 21 demographic and co-morbid factors, was used to predict the number of expected mortalities at each hospital. The number of risk-adjusted lives saved (LS) was calculated for each hospital as the difference between the number of observed deaths and the risk-adjusted expected number of deaths. Statistical differences in the average number of LS and LS per 1,000 patients between hospitals in the two study groups were compared using the Student T-test and Pearson Correlation Coefficients.

Results: The Table indicates that 17 (31%) of the 54 HCA hospitals do not routinely use CRNAs during OPCAB surgery. The table also indicates that hospitals not routinely using CRNAs performed significantly more CABG surgeries and had significantly ($p<0.05$) better average outcomes (more LS and LS per 1000 patients) than those hospitals routinely using CRNAs. There was no statistically significant difference in percent of CABG surgeries performed off pump between hospitals in the two groups. Finally, the estimated Pearson Correlation Coefficient between the indicator variable that a hospital routinely used CRNAs and the hospital's risk-adjusted number of LS and risk-adjusted number of LS/1000 was -0.31 ($p=0.023$) and -0.28 ($p=0.037$), respectively.

Conclusions: This study provides preliminary evidence that hospitals routinely using anesthesiologists during OPCAB surgery have better risk-adjusted CABG surgery survival rates. However, future research needs to adjust for other structural and process factors that may be related to outcomes.

Is the Routine Use of Certified Registered Nurse Anesthetists Associated with a Hospital's Risk-Adjusted CABG Surgery Survival Rates?

	Do Not Use CRNAs	Use CRNAs	p-Value
Number of Hospitals	17	37	
Average CABG Surgeries	292±135	195±131	0.016
Risk-Adjusted LS	1.27	-0.64	0.023
Risk-Adjusted LS/1000 Patients	3.56	-5.07	0.015
% Surgeries Off Pump	25.6%	36.5%	0.610

SCA39

HYPOTENSION DURING CARDIOPULMONARY BYPASS IS NOT ASSOCIATED WITH COGNITIVE DECLINE AFTER CABG

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Introduction: Neurocognitive dysfunction (NCD) continues to occur in a significant number of patients after cardiopulmonary bypass (CPB) [1]. The factors influencing its incidence and severity are not completely known. Systemic hypotension during CPB has been suspected as a contributing factor in post-cardiac surgery NCD, although its role has been incompletely studied. We investigated the relationship between hypotension during CPB and postoperative NCD.

Methods: Following IRB approval, we identified patients who participated in non-interventional studies of NCD. All patients underwent CABG surgery utilizing CPB during 1993-2004. Invasive mean arterial blood pressure (MAP) was recorded every 30-60 seconds using automatic anesthesia record keeping. Baseline MAP was defined as the median MAP over the first three minutes of the case. The hypotensive burden during CPB was quantified by the area less than 50 mm Hg on a MAP vs. time curve (MAP area<50). Neurocognitive testing was performed both preoperatively (baseline) and 6 weeks after surgery, and an overall cognitive score was calculated by factor analysis [1]. Effects on six-week change in cognitive score were analyzed by multivariable linear regression. A dichotomous neurocognitive deficit was defined as a drop of greater than one standard deviation from baseline on any of the 4 cognitive factors; this was analyzed using multivariable logistic regression.

Results: 590 patients had both 6-week cognitive testing and adequate MAP data available and are included in this analysis. Table 1 describes their demographic characteristics. A scatter plot of cognitive change versus MAP area<50 displays the lack of association between these two variables (Figure 1). This was corroborated by a multivariable regression analysis, even when controlling for baseline MAP (p=0.62; see Table 2). Similarly, no effect of MAP area<50 was seen on the dichotomous neurocognitive deficit outcome (p=0.39).

Discussion: The effect of hypotension during CPB on post-CABG NCD has not been adequately defined. This well-powered study indicates that the hypotensive burden during CPB is not associated with the incidence or severity of cognitive change after CABG.

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Table 1: Study Sample Demographics (N=590)

	Mean	SD
Age at Surgery	61.8	10.4
Years of Education	12.7	3.3
# of Grafts	3.2	0.9
LV Ejection Fraction (%)	53.6	11.7
CPB Time (minutes)	110.9	33.8
Aortic Cross-Clamp Time (minutes)	59.2	22.6
Baseline Mean Arterial Pressure (mm Hg)	94	15.2
MAP minutes <50 mm Hg	24	23.3
	Count	Percent
Race (% Caucasian)	510	86.4
Gender (% Female)	139	23.6
Diabetes (%)	165	28.0
History of Hypertension	370	62.9
6-Week Cognitive Deficit	228	38.6

Table 2: Multivariable Regression Model of 6 Week Cognitive Change
Overall model p <0.0001 (F=9.41, R-square= 0.1024)

Variable	Beta Estimate	t Statistic	p- Value
Baseline Cognitive Score	-0.214	-7.26	<.0001
Age at surgery	-0.00584	-5.05	<.0001
Years of Education	0.00953	2.48	0.0135
Diabetes	-0.0433	-1.76	0.0782
Caucasian vs Any Other	0.102	2.97	0.0031
MAP area <50	0.00003	0.50	0.6192
Baseline MAP	-0.0007	-0.97	0.3318

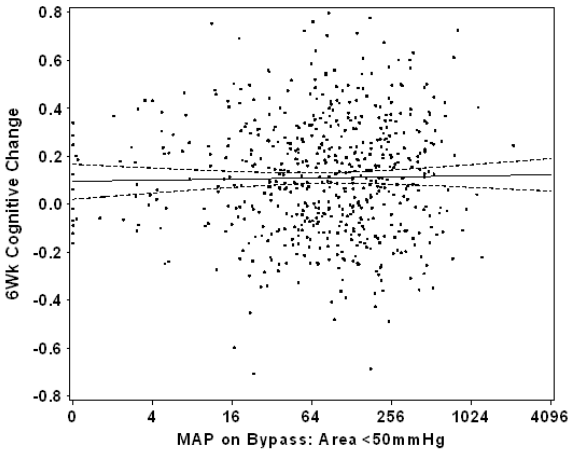

Figure 1: Scatter Plot of 6 Week Cognitive Change versus MAP area <50 mm Hg with 95% confidence levels for the regression line.

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INCREASED PKA-MEDIATED PHOSPHORYLATION OF MYOCARDIAL BETA-2 ADRENERGIC RECEPTORS IN A LARGE ANIMAL MODEL OF CHRONIC HEART FAILURE

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Introduction: Chronic heart failure (CHF) is characterized by deranged beta-adrenergic receptor (βAR)/Gsα signal transduction. The G proteins Gsα and Gαi-2 regulate cardiac inotropy via stimulation and inhibition of adenylyl cyclase, respectively. The role of increased Gαi-2 in CHF remains unknown. Gαi-2 may activate cardiac antiapoptotic pathways via MAP kinase signal transduction. βARs undergo negative feedback inhibition by phosphorylation by PKA or BARk. Protein kinase A (PKA)-mediated phosphorylation of β2AR (PKA-p-β2AR) alters coupling of β2AR to favor Gαi-2 over Gsα in cell culture. It is unknown if PKA-p-β2AR couples to Gαi-2 to activate these survival pathways. While this association has been demonstrated in vitro (1), PKA-p-β2AR has not been demonstrated in-vivo. Gαi-2 is increased in CHF myocardium (2) and may preferentially couple PKA-p-β2AR to Gαi-2, resulting in contractile inhibition. We therefore test the hypotheses that myocardial PKA-p-β2AR increases in CHF and correlates with increased Gαi-2 protein in a large animal model of CHF (3).

Methods: CHF was induced in sheep via microembolization of the circumflex coronary artery (LCx) (3). Left ventricular (LV) myocardium was obtained from 4 CHF sheep (LV ejection fraction <35% for ~20 months) and 4 control sheep. Immunohistochemistry and western blots were performed with antisera specific for Gαi-2 and PKA-p-β2AR at the PKA phosphorylation site. Protein bands were quantified using densitometry.

Results: Microembolization of the LCx resulted in ischemia/fibrosis (LV posterior wall). EF decreased from 51±3% to 23±5%. PKA-p-β2AR increased 24% in CHF compared to controls. Gαi-2 significantly increased 6.4-fold in the CHF compared to controls. PKA-p-β2AR positively correlated to Gαi-2 protein levels (p=0.0146) in CHF but not in controls. Immunohistochemistry revealed increased PKA-p-β2AR and disorganized distribution in CHF compared to controls.

Conclusions: PKA-p-β2AR is increased in an ovine model of CHF. PKA-p-β2AR positively correlated to Gαi-2 protein levels in CHF. Increased PKA-p-β2AR may promote increased coupling to Gαi-2. This is the first study to demonstrate increased PKA-p-β2AR and correlate upregulation of PKA-p-β2AR with Gαi-2 in vivo, a prerequisite if putative antiapoptotic pathways are functional. Failing myocardium may be forced to choose between acute transient inotropic augmentation via βAR/Gsα pathways at the expense of continued receptor desensitization. Alternatively, PKA-p-β2AR may provide santuary to the β2AR by allowing it to couple to Gαi-2 with the potential activation of survival pathways for long-term benefit of cardiac function.

References:

1) J Biol Chem 2002;277:31249.
2) Anesth Analg 2005;100:S-340.
3) J Card Fail 2004;10:174.