

SCA1
APROTININ USE AND RED BLOOD CELL
TRANSFUSION IN OFF-PUMP BILATERAL LUNG
TRANSPLANTATION

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Introduction: Red blood cell (RBC) transfusion may contribute to overall morbidity and mortality (1). In lung transplantation, aprotinin has been shown to reduce RBC transfusion when performed with cardiopulmonary bypass (CPB) (2). However, off-pump lung transplantation is becoming the standard of care and the efficacy of aprotinin in this setting has not been studied. Therefore, our objective was to determine whether aprotinin use will decrease intraoperative RBC transfusion in off-pump bilateral orthotopic lung transplantation (OP-BOLT).

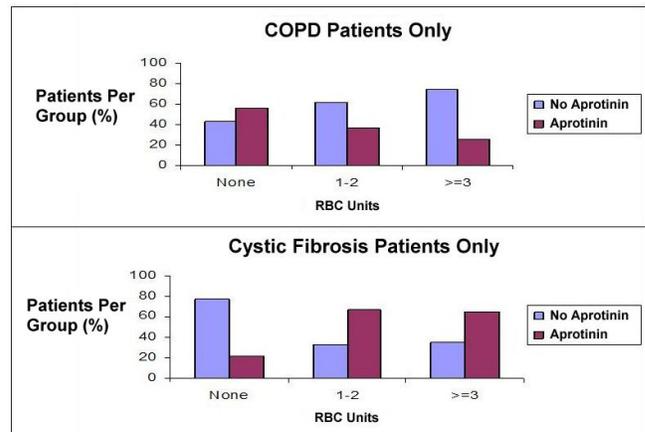
Methods: After IRB approval, we completed a retrospective chart review of all adult OP-BOLT's done between January 2000 and January 2005 at a single university center (n=158). The 4 most common preoperative diagnoses were included: chronic obstructive pulmonary disease (COPD, n=71), cystic fibrosis (CF, n=41), idiopathic pulmonary fibrosis (n=37), and sarcoidosis (n=9). Exclusions were re-do lung transplantation and the use of CPB. The decision to use aprotinin was determined by the attending anesthesiologist and it was started at the time of induction at the recommended dose used during cardiothoracic surgery. The decision to transfuse was determined by the attending anesthesiologist. The primary outcome variable was RBC transfusion in the OR. Clinical covariates included the primary diagnosis, sex, height, weight, previous thoracotomy status, and the following preoperative labs: hemoglobin, activated partial thromboplastin time, international normalized ratio, and platelet count. An ordinal logistic regression model, adjusting for covariate predictors of transfusion, was utilized to analyze the data.

Results: Eighty patients received aprotinin (aprotinin group) and 77 did not (non-aprotinin group). Clinical covariates were similar for both groups. Only weight (p=0.004) was found to be a significant predictor of RBC transfusion. Overall, there was no difference in RBC transfusion between the aprotinin and non-aprotinin groups. However, investigation of interaction terms between diagnosis subgroups and aprotinin use revealed that the COPD group that received aprotinin showed a reduction in RBC transfusion (p=0.03) and the CF group that received aprotinin showed an increase in RBC transfusion (p=0.01) (figure 1).

Conclusion: Our results in OP-BOLT show a significant reduction in RBC transfusion in the OR when aprotinin was used in our largest transplanted group, COPD. This is consistent with previously observed effects of aprotinin use on bleeding in thoracic surgery (3). It is unclear whether a residual confounding factor led to the use of aprotinin in CF patients who were at a higher bleeding risk or if a true paradoxical effect of aprotinin was observed in this group. Further prospective study should investigate this observation.

References

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SCA2

**CARDIAC FUNCTION AND ACUTE LUNG INJURY
AFTER THORACIC SURGERY**

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Background: The effects of major lung resection on heart function and occurrence of acute lung injury (ALI) have not been well established. Our goal was to study right and left heart function early after thoracic surgery using Doppler echocardiography at a time usually preceding ALI.

Methods: Using a prospective database, we examined the records of 279 patients who had thoracic surgery and had transthoracic echocardiography performed on postoperative day 1-4 as part of a larger research effort. ALI was defined as acute respiratory failure requiring intubation within 30-days of surgery. Data were analyzed with Fisher's exact or Wilcoxon rank sum tests.

Results: ALI occurred in 13/279 (4.7%) of patients. Pneumonia occurrence was strongly associated with ALI 6/13 (46%) vs. 9/266 (3.4%) with no ALI, $P < 0.0001$. Except for a trend of a lower DLCO-ppo. among ALI patients ($P=0.08$), those with or without ALI did not differ in any clinical or echocardiographic variable measured, Tables 1 and 2. Indices of left or right heart function were within the normal range in both groups, Table 2.

Conclusion: Early postoperative indices of left or right heart function did not differ in patients with or without ALI. The occurrence of pneumonia after lung resection appears to be a strong predictor of ALI.

Table 1: Patient Characteristics.

	ALI (n=13)	No ALI (n=266)	P Value
Age, yr.	65 ± 11	61 ± 11	0.26
Male (%)	9 (69)	155 (58)	0.56
Hypertension (%)	3 (23)	56 (21)	0.74
Coronary Artery Disease (%)	0 (0)	14 (5)	0.99
Diabetes Mellitus (%)	2 (15)	16 (6)	0.20
FEV1 % ppo.	41±19	47±23	0.33
DLCO % ppo.	36±21	47±25	0.08
Operation type			0.63
Wedge resection (%)	1 (8)	22 (8)	
Lobectomy (%)	4 (31)	116 (44)	
Pneumonectomy (%)	8 (62)	128 (48)	

Data are mean ± SD or n (%). ppo- predicted postoperative.

Table 2: Echocardiographic Data.

	ALI (n=13)	No ALI (n=266)	P Value
Heart rate, bpm	101 ± 20	92 ± 16	0.16
IVC-p, mmHg	4.1 ± 3.9	4.5 ± 3.6	0.19
Left atrial size, cm	4.2 ± 0.8	4.4 ± 0.9	0.49
Right atrial size, cm	4.6 ± 0.6	4.6 ± 0.7	0.96
TR-Jet, m/s	2.2 ± 0.6	2.2 ± 0.6	0.88
LVEF, %	62 ± 8	63 ± 10	0.84

IVC-p: inferior vena cava estimated right atrial pressure; TR-Jet: tricuspid regurgitation jet velocity; LVEF: left ventricular ejection fraction.

SCA3

COMBINED CLOPIDOGREL AND ASPIRIN THERAPY IN PATIENTS UNDERGOING CAROTID ENDARTERECTOMY IS ASSOCIATED WITH AN INCREASED RISK OF POSTOPERATIVE BLEEDING

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Introduction: Clopidogrel (Plavix), a potent inhibitor of ADP-induced platelet aggregation, may reduce the risk of stroke in carotid endarterectomy (CEA) patients [1]. However, clopidogrel administration may also significantly increase postoperative blood loss after cardiovascular surgery [2,3]. We investigated whether combined preoperative clopidogrel and ASA therapy in patients undergoing CEA improves in-hospital outcomes without increasing postoperative bleeding.

Methods: All patients who underwent CEA (n=1518) between 01/01/98 and 01/06/05 at our institution were classified by preoperative treatment type: clopidogrel and ASA (n=323), ASA only (n=651), or no oral antiplatelet therapy (n=527). Patients with concomitant cardiac surgery or preoperative clopidogrel therapy only were excluded. Patient demographics and risk factors were abstracted from our database and entered into a multivariate regression analysis to determine whether combined preoperative clopidogrel and ASA administration is independently associated with improved outcomes after CEA. The discriminatory power of the multivariate model was quantified by the c-index.

Results: Combined preoperative clopidogrel and ASA therapy did not reduce the risk of 30-day mortality, cardiac arrhythmia, MI, cardiac arrest, low-output syndrome, stroke, respiratory failure, renal dysfunction, need for reoperation, or length of hospital stay (Table 1). In contrast to single ASA therapy, combined preoperative clopidogrel and ASA therapy was independently associated with a nearly 5-fold higher risk of postoperative bleeding (OR=5.1; 95% CI=1.8-14.1; Figure 1). The majority of these bleeding episodes required surgical intervention (OR=3.2; 95% CI=1.2-10.1).

Conclusion: Combined preoperative clopidogrel and ASA administration did not significantly reduce any measured adverse clinical outcome. Moreover, the combined risks of perioperative transfusion and need for reoperation may outweigh the risks of discontinuing preoperative ADP-induced antiplatelet therapy.

References

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2. Payne, D.A., et al., Combined therapy with clopidogrel and aspirin significantly increases the bleeding time through a synergistic antiplatelet action. *J Vasc Surg*, 2002. 35:1204-9.
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Perioperative Demographics and Risk Factors	Clopidogrel/ASA Therapy (n=323)	ASA Therapy (n=651)	No Anti-platelet Therapy (n=527)	P-value (χ^2)
30-Day Mortality (%)	0.31	0.77	0.76	0.67
Myocardial Infarction (%)	0.00	0.15	0.38	0.46
Cardiac Arrest (%)	0.93	0.61	0.57	0.80
Atrial Flutter (%)	0.00	0.00	0.57	0.06
Atrial Fibrillation (%)	1.24	1.08	1.52	0.79
Ventricular Tachycardia (%)	0.31	0.92	1.52	0.22
Ventricular Fibrillation (%)	0.31	0.15	0.38	0.75
Low Output Syndrome (%)	1.24	2.00	1.33	0.56
Stroke (%)	1.86	2.46	3.23	0.46
Respiratory Failure (%)	0.00	0.92	1.52	0.08
Renal Failure (%)	0.62	0.77	1.14	0.68
Infection (%)	0.31	0.31	0.00	0.44
Bleeding (%)	4.33*	0.92	1.14	0.0003
Re-operation due to Bleeding (%)	2.48*	0.46	0.95	0.01
Length of Hospital Stay (d)	3.4±3.1	3.7±4.5	4.1±4.3	0.39

Table 1: Incidence of adverse postoperative outcomes following CEA in patients receiving combined preoperative clopidogrel/ASA therapy, ASA only, or not receiving anti-platelet therapy.

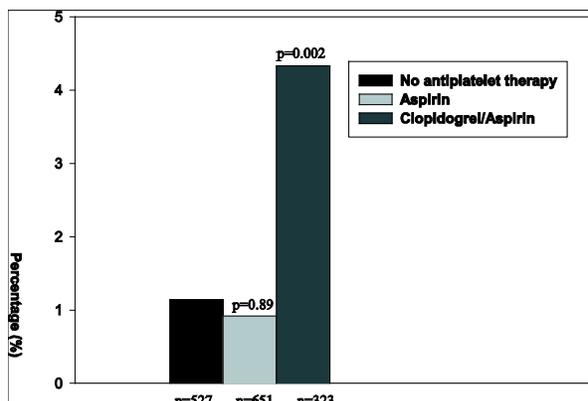


Figure 1: Significantly increased risk of Clopidogrel-associated postoperative bleeding when compared to Aspirin and non antiplatelet therapy. Incidence of postoperative bleeding (%) and p-values according to each subgroup are shown.

SCA4
INTENSE CARDIAC TROPONIN SURVEILLANCE
FOR LONG-TERM BENEFITS IS COST-EFFECTIVE
IN PATIENTS UNDERGOING ABDOMINAL AORTIC
SURGERY

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Introduction: Recent studies suggest that preoperative coronary revascularization before elective vascular surgery does not alter the long-term outcome. Early recognition and treatment may be a key strategy to reduce cardiac risk. Cardiac troponin I (cTnI) screening is an effective means of surveillance for perioperative myocardial infarction (MI).[1] The cTnI surveillance has allowed recognition of two distinct patterns (i.e. early and delayed) of MI in patients undergoing abdominal aortic surgery.[2] The cTn measurement has long-term prognostic value with regard to cardiac outcomes and mortality after vascular surgery.[3]

Methods: We designed a Markov based decision analysis model to determine the cost-effectiveness of routine postoperative surveillance with cTnI on days 0,1,2,3 with an aim to institute risk-reducing strategies in patients screened positive. The cut-off value for cTnI intervention was 1.5 ng/ml. Key baseline input variables included the following: sensitivity and specificity of cTnI 0.80 and 0.93 respectively, probability of MI: 0.049, probability of death in patients who suffered MI: 0.22, probability of death in others: 0.033.[2] Other variable assumptions include the following: cost of troponin: \$357, cost and efficacy of risk reducing strategies: \$11,390 (five days of ICU management) and 0.47 respectively. Annual rates for future MI and coronary revascularization in those who suffered MI:

0.076 and 0.037 and in those who did not suffer MI: 0.012 and 0.012 respectively. Base-case was "standard-care" management without cTnI surveillance. The time horizon was life-time and the target population being individuals aged 65 years (median) undergoing elective open abdominal aortic surgery. Long-term survival was modeled using US life tables while incorporating excess mortality rates associated with different states in the decision tree. Medicare reimbursement cost data were used to reflect societal perspective for analysis. Future costs (in 2003 US dollars) and QALYs were discounted at a 3% annual rate. Sensitivity analysis also included multivariate second-order Monte Carlo simulation for incremental cost-effectiveness ratio (ICER) values.

Results: Baseline analysis is listed in the table.

Monte Carlo analysis with 10,000 simulations revealed median (2.5% and 97.5%) ICER values to be \$22,434 (\$11,796 and \$52,122).

Discussion: In patients presenting for elective open abdominal aortic surgery, routine intensive surveillance with cTnI and early institution of treatment is cost-effective for long-term benefits when interpreted by comparing with published ICERs for commonly funded interventions.

References:

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2. Le Manach Y et al. *Anesthesiology* 2005; 102: 885-91
3. Landesberg et al. *J Am Coll Cardiol* 2003; 42: 1547-54

Table

Strategy	Costs	QALYs	ICER (cost/QALY)
Standard care	\$27,992	10.4577	
cTnI surveillance	\$29,472	10.5709	\$13,250

SCA5

PERIOPERATIVE CHANGES IN RED BLOOD CELL DEFORMABILITY IN PATIENTS UNDERGOING MAJOR NON-CARDIAC SURGERY: PRELIMINARY RESULTS

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Background: Morbidity in high-risk surgical patients is responsible for increased length of stay (LOS) and hospital costs. There is growing evidence that altered microcirculatory flow is a causative factor in the development of organ dysfunction, and that changes in erythrocyte deformability may play a critical role. (1-3) In contrast to micropipette or cell-transit time, laser-assisted optical rotational red cell analyzer (LORCA) is one of the few established assays that can be used to quickly measure RBC deformability in a large number of clinical samples. In only 4 minutes, a blood sample is subjected to 9 different shear stresses (0.3 to 30 Pa) and an elongation index (EI) is calculated for each sample with $EI = (A-B)/(A+B)$.(4) It is not known if RBC deformability changes in the perioperative period. Therefore, we sought to assess these potential changes in a diverse group of non-cardiac surgical patients.

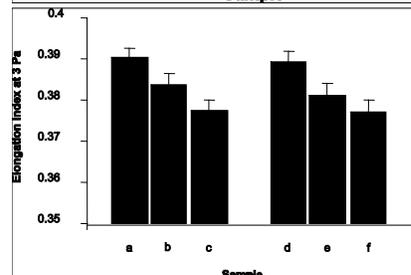
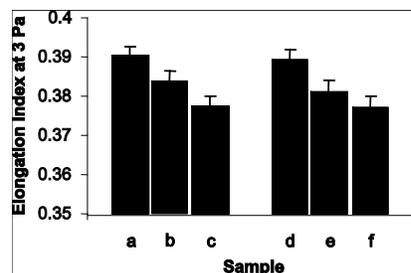
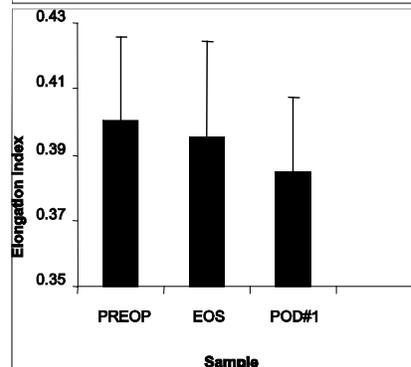
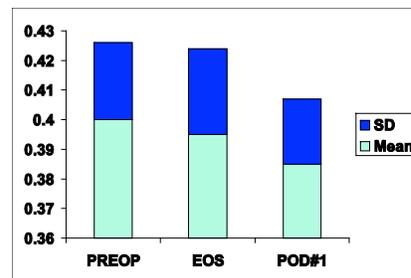
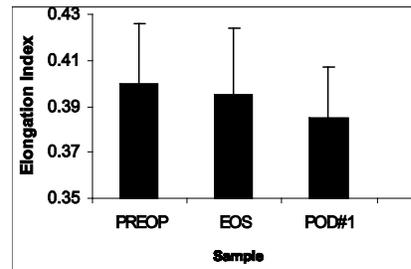
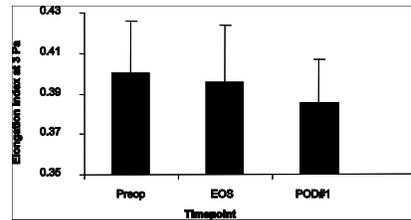
Methods: As part of an ongoing IRB-approved study, 25 subjects undergoing a diverse group of non-cardiac surgical procedures were enrolled in the study. Blood was collected preoperatively, at the end of surgery (EOS), and on post-operative day #1 (POD1). All samples were collected in 4 cc Vacutainer tubes (K2 EDTA). Using a single LORCA device blood was assayed according to manufacturer's instructions.

Results: The figure shows EI at the study time points (mean \pm SD). Statistically significant ($p=0.0059$) decreases in deformability were observed between preoperative and post-operative day #1 values. There was little difference observed between preoperative and end of surgery samples.

Conclusion: In patients undergoing major non-cardiac surgery, there is a statistically significant decrease in erythrocyte deformability observed on post-operative day #1. Values at the end of surgery, however, were similar to baseline. The association of these changes to postoperative morbidity and organ dysfunction will be assessed once enrollment is complete in this study.

References:

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3. Piagnerelli et al. Intensive Care Med. 2003; 29: 1052-61
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SCA6

APROTININ USE AND ALLOGRAFT FUNCTION AFTER OFF-PUMP BILATERAL LUNG TRANSPLANTATION

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Introduction: In lung transplantation, ischemia-reperfusion injury (IRI) contributes to primary graft dysfunction, a marker for mortality (1). In an animal model of lung transplantation, aprotinin appears to attenuate IRI when added to the lung preservation solution (2). Furthermore, aprotinin may be beneficial in lung transplantation by reducing bleeding, transfusion requirement, and related lung injury, which may also impact mortality (3). However, aprotinin use without the relative coagulopathy associated with cardiopulmonary bypass (CPB) may predispose the off-pump patient to thrombotic complications (4); and since off-pump lung transplantation is becoming the standard of care, the impact of aprotinin use in this setting is unknown. Therefore, we tested the hypothesis that aprotinin use will have no immediate effect on allograft function after off-pump bilateral orthotopic lung transplantation (OP-BOLT).

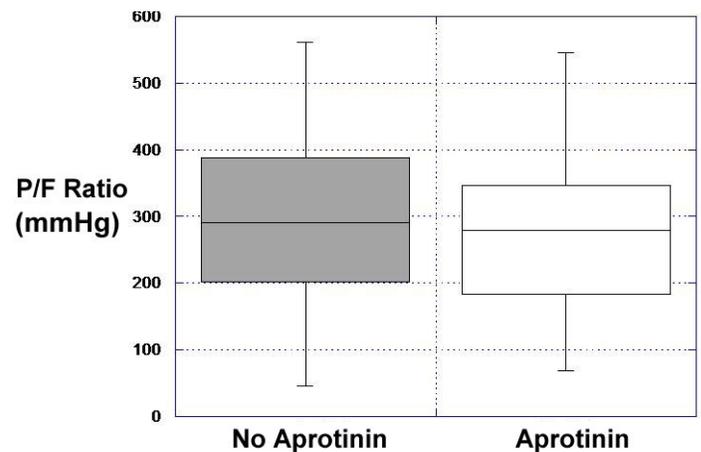
Methods: After IRB approval, we completed a retrospective chart review of all adult OP-BOLT's performed between 2000 and 2005 at a single university center (n=158). The 4 most common preoperative diagnoses were included: chronic obstructive pulmonary disease (n = 71), cystic fibrosis (n=41), idiopathic pulmonary fibrosis (n=37), and sarcoidosis (n=9). Exclusions were re-do lung transplantation and the use of CPB. The decision to use aprotinin was determined by the attending anesthesiologist. Aprotinin was started at the time of induction and was administered at the recommended dose used during cardiothoracic surgery. The primary outcome variable was PaO₂/FiO₂ (P/F) ratio at the end of surgery. Clinical covariates included inhaled nitric oxide use and allograft ischemic time. A multivariable linear regression model was utilized to analyze the data.

Results: Eighty patients received aprotinin (aprotinin group) and 77 did not (non-aprotinin group). The unadjusted effect of aprotinin use on the P/F ratio is illustrated in figure 1. There was no difference in P/F ratios by diagnosis or inhaled nitric oxide use. However, allograft ischemic times differed between the aprotinin and non-aprotinin groups (p=0.02). Therefore, the model was adjusted for ischemic time, which showed no main effect of aprotinin (p=0.47) or ischemic time (p=0.22). There was no interaction between aprotinin use and ischemic time (p=0.65).

Conclusion: In our study, there were no differences in the end of surgery PaO₂/FiO₂ ratios between the aprotinin and the non-aprotinin groups undergoing off-pump bilateral lung transplantation. These results suggest no immediate benefit or risk from aprotinin use with regards to immediate allograft function. This merits confirmation with prospective study including postoperative allograft function.

References

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SCA7

DIAGNOSIS AND ASSESSMENT OF PERIOPERATIVE DIASTOLIC DYSFUNCTION DURING ELECTIVE ABDOMINAL AORTIC ANEURYSM REPAIR AND ITS ASSOCIATION WITH MORBIDITY AND MORTALITY

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Introduction: Transmitral Color M-Mode flow propagation velocity (Vp) obtained through transesophageal echocardiography (TEE) has been shown to be a valuable tool in the assessment of perioperative diastolic dysfunction¹. We compared Canadian Consensus Guidelines² (CCG) for classification of diastolic function and Vp in predicting outcome.

Materials and Methods: All patients undergoing elective open repair of abdominal aortic aneurysm were considered eligible. After induction of general anesthesia, TEE exam was performed and mitral valve and left atrial (LA) inflow patterns were recorded with pulse wave Doppler (PWD) before (baseline), during and after application of the aortic cross clamp and Vp was recorded simultaneously. Diastolic dysfunction according to the CCG was graded as 1 for normal, 2 for mild, 3 for mild-to-moderate, 4 for moderate and 5 for severe diastolic dysfunction and 0 value was assigned for inconclusive results. A Vp value of less than .4m/sec was considered consistent with diastolic dysfunction.

Results: Thirty patients (M:F=22:8), aged 64 +/- 11.9 years, were enrolled. Their co-morbidities were hypertension in 50%, diabetes mellitus in 20%. 50% had been on a beta-blocker preoperatively, but all received beta-blockade perioperatively. The aorta was cross-clamped for an overall average duration of 78  28”.

In 10 patients Vp could not be recorded and 3/30 had inconclusive data by CCG. 14/30 patients had normal diastolic function by CCG and 2/20 by Vp throughout the procedure. Vp diagnosed all the patients with diastolic dysfunction that were diagnosed by CCG and additional six patients in which the CCG was either normal or inconclusive.

Six patients had postoperative cardiac complications (20%). There was one death postoperatively (3.3%), 3 had postoperative

CHF (20%) and 1 myocardial infarction (MI) (3.3%), and 1 patient had postoperative atrial fibrillation with hemodynamic instability. We assessed for a relationship of CCG and Vp for a combined outcome of death, congestive heart failure or post-operative arrhythmia. CCG were normal throughout the procedure for 4 patients who had postoperative complications and diagnosed diastolic dysfunction only in 2 patients. We did not find a significant relationship between either a Vp of <0.4 or a CCG of greater than 1 (p>0.05). It is possible to assign a severity grade to diastolic dysfunction by CCG, whereas Vp is a categorical measure only. Ongoing study will be necessary to identify such a relationship and assess severity grade in Vp.

Number	Gender	Pre Clamp CCG	Pre Clamp VP	Clamp CCG	Clamp Vp	Post Clamp CCG	Post Clamp Vp	Complications
1.	F*	1	NA	1	NA***	1	NA	
2.	F	1	NA	2	NA	1	NA	
3.	M ^{oo}	3	NA	3	NA	2	NA	DEATH
4.	M	1	NA	1	NA	1	NA	
5.	F	1	.5m/s	1	.6m/s	1	.6m/s	
6.	M	1	.3m/s	1	.4m/s	1	.4m/s	AF*
7.	M	1	NA	1	NA	1	NA	CHF**
8.	M	1	.4m/s	2	.4m/s	2	.4m/s	
9.	M	1	NA	4	NA	1	NA	
10.	M	1	NA	1	NA	1	NA	
11.	M	1	NA	1	NA	1	NA	
12.	M	1	NA	1	NA	1	NA	
13.	M	1	.4m/s	1	.4m/s	1	.3m/s	CHF**
14.	M	2	.4m/s	3	.25m/s	2	.3m/s	
15.	M	1	.5m/s	1	.5m/s	1	.5m/s	
16.	M	1	.5m/s	1	.3m/s	1	.5m/s	CHF**
17.	M	1	1.2m/s	1	.2m/s	1	.5m/s	
18.	F	4	.3m/s	4	.3m/s	4	.4m/s	
19.	F	4	.2m/s	4	.3m/s	4	.4m/s	
20.	M	1	.4m/s	1	.2m/s	1	.3m/s	
21.	F	1	.5m/s	1	.3m/s	1	.5m/s	
22.	F	1	.5m/s	4	.3m/s	1	.6m/s	
23.	M	1	.2m/s	0	.3m/s	1	.3m/s	
24.	F	4	.2m/s	4	.3m/s	4	.2m/s	
25.	M	0	.3m/s	0	.3m/s	0	.3m/s	
26.	M	3	.2m/s	1	.3m/s	0	.2m/s	
27.	M	0	.2m/s	0	.3m/s	0	.3m/s	
28.	M	3	.3m/s	3	.3m/s	4	.3m/s	
29.	M	3	.3m/s	3	.3m/s	3	.3m/s	MI***
30.	M	0	NA	0	NA	0	NA	

*Atrial Fibrillation
** Congestive Heart Failure
*** Myocardial Infarction
**** Not available
* Female
oo Male

SCA8
ANESTHETIC PROBLEM-SOLVING FOR
ENDOVASCULAR REPAIR OF A GIANT INNOMINATE
ARTERY PSEUDOANEURYSM ERODING INTO A
MEDIASTINAL TRACHEOSTOMY

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Introduction: We describe emergency endovascular repair of a leaking giant innominate pseudoaneurysm (IPA). The anesthetic plan required no airway manipulation, cardiopulmonary bypass (CPB), and precise control of anesthetic depth. To our knowledge, this is the first report of endovascular non-traumatic IPA repair with CPB

Clinical Presentation: A 16-year old boy presented with hemoptysis secondary to a giant IPA. He had received radiation for mediastinal lymphoma. He later developed tracheal stenosis and tracheal-innominate fistula. Definitive surgical management required ligation of the innominate artery and mediastinal tracheostomy. A giant IPA subsequently resulted; it was initially managed with endovascular coil embolization.

During this presentation, aortography confirmed flow into the IPA with dispersed coils. Repeat embolization or open surgical management was deemed too high-risk. After extensive discussion, endovascular exclusion of the IPA was selected. Anesthetic monitoring consisted of routine ASA monitors, a dorsalis pedis arterial line and EEG. Flow-by oxygen at 6 liters per minute was administered. A 20G peripheral intravenous line was established. The patient was sedated with titrated ketamine (5-10mg per bolus) after preoperative midazolam and glycopyrrolate.

Under local anesthesia, the left femoral vein was cannulated for large-bore central venous access. After heparin administration,

the right femoral artery and vein were cannulated and CPB was initiated. General anesthesia was then induced with titrated propofol (2mg/kg total). The patient subsequently received scopolamine 0.4 mg and a remifentanyl infusion at 0.5-1.0 mcg/kg/min. Neuromuscular blockade was achieved with vecuronium (0.1mg/kg) and subsequently titrated for a train-of-four ratio of 25%.

The endovascular stent (ES) design was for abdominal deployment and so was too short for a left iliac artery approach. After considerable dissection, the left axillary artery was deemed too small for stent deployment. The remaining arterial approach was the left common carotid artery (LCCA).

To provide cerebral flow during ES deployment, the left internal carotid artery was cannulated and connected to the arterial cardiopulmonary bypass circuit. With antegrade cerebral perfusion accomplished, the ES was deployed through the LCCA to exclude the IPA and spare the origin of the LCCA. These findings were confirmed during completion angiography. There were no EEG changes.

Prompt emergence from general anesthesia was then achieved after termination of the remifentanyl infusion, and administration of physostigmine and neuromuscular reversal. After adequate spontaneous ventilation had resumed, the patient was rapidly weaned from CPB. The remaining hospital course was uneventful.

Discussion: This unusual airway at high risk for exsanguinating hemoptysis prompted airway management with CPB and a no-touch technique. The anesthetic plan must remain flexible and accommodating especially in unusual and emergency circumstances.

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SCA9
NITROSATIVE STRESS ASSOCIATED WITH SINGLE LUNG VENTILATION AND PULMONARY RESECTION IMPAIRS MYOCARDIAL CALCIUM CYCLING

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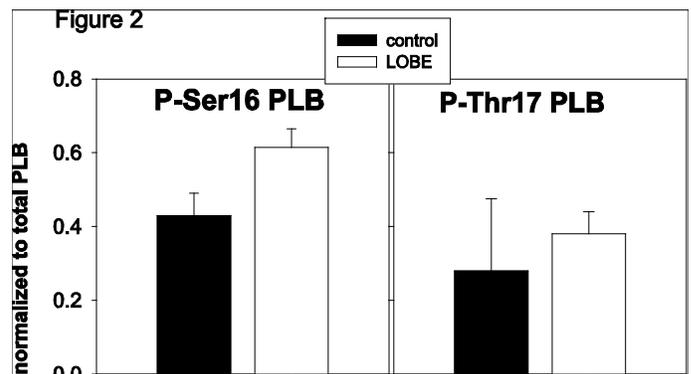
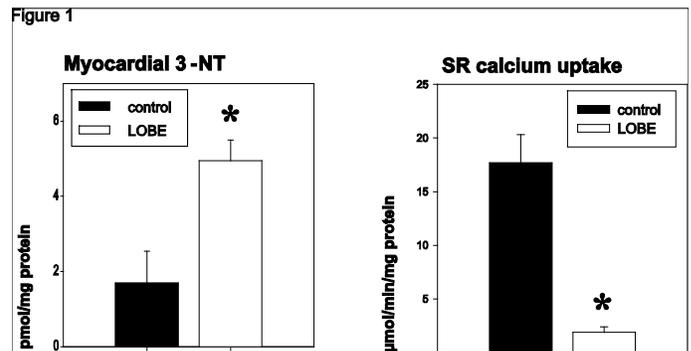
Recent data suggest that pulmonary resection during single lung ventilation elicits a systemic oxidative challenge that persists postoperatively (1). Additional studies have indicated that, within the heart, oxidative/nitrosative stress resulting from chronic disease can have direct effects on myocyte calcium cycling (2). In particular are data demonstrating that peroxynitrite (ONOO-) mediated nitration of the key calcium cycling protein sarcoplasmic endoreticular calcium ATPase subtype 2a (SERCA2a) impairs protein function and may contribute to diminished inotropy and lusitropy in dilated myopathy (2). The present study was designed to test the hypothesis that oxidative/nitrosative stress associated with pulmonary resection during single lung ventilation in otherwise healthy subjects can mimic the reported effects of chronic disease on SERCA2a activity.

Methods: Myocardial tissue harvested from 12 swine were used for the study; 7 animals had undergone left upper lobectomy 3 days prior to tissue harvest (LOBE) while the other 5 were non-operated controls. Within each group, myocardial ONOO-generation (reflecting the reaction of superoxide with nitric oxide) was quantified by HPLC measurement of protein 3-nitrotyrosine (3-NT) content. Attendant changes in SERCA2a expression and function were determined from Western blotting and analysis of indo-1 uptake by isolated sarcoplasmic reticular membranes, respectively. In addition, since SERCA2a activity is regulated by the phosphorylation state of phospholamban (PLB), phosphorylation at serine 16 (P-Ser16) and threonine 17 (P-Thr17) of PLB was determined by Western blotting. Control vs LOBE differences were compared by t-test. Data are presented as mean [SPCHAR(plusmn)] SE, and for all statistical tests, a $p < 0.05$ was considered significant (* in figures).

Results: There was a distinct difference in myocardial 3-NT between control and LOBE animals that was associated with a marked reduction in calcium uptake by SERCA2a (figure

1). This decline in SERCA2a activity was not coincident with altered expression of SERCA2a (1.2[SPCHAR(plusmn)]0.1 vs 1.1[SPCHAR(plusmn)]0.1) or decreased PLB phosphorylation (figure 2).

Conclusion: These data strongly support the probability that perioperative oxidative/nitrosative stress associated with lung resection can influence SERCA2a activity independent of any influence on protein expression or phosphorylation of the SERCA2a regulator PLB. Importantly, these are the first data to link an acute event with a subcellular process previously described only in chronic illness.



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SCA10

DETECTION OF LOW PLASMA LEVELS OF LOW MOLECULAR WEIGHT HEPARIN

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Introduction: The detection of low-molecular-weight (LMWH) heparin in blood is complicated by the fact that it is refractory to neutralization by protamine. Thromboelastographic analysis has demonstrated that the anticoagulant effect of LMWH can be reversed by heparinase I(1). Although LMWH can be formed by controlled digestion of unfractionated heparin with heparinase, more prolonged digestion appears to result in complete loss of anticoagulant activity. In an effort to develop a relatively simple and rapid test for detection of effective levels of LMWH, we utilized a test-tube coagulation assay, Hemochron Saline (HS), which contains no activators of coagulation. In previous studies, the HS assay proved sensitive to detection of low levels of unfractionated heparin and protamine excess (2,3). The HS assay is carried out in a small, battery-operated apparatus and is fully automated. After a comparison of the sensitivities of HS, activated partial thromboplastin time (aPTT) and thrombin time (TT) to enoxaparin anticoagulation, we tested the extent of reversal of the enoxaparin effect in the HS assay, after digestion with heparinase.

Methods: In the initial studies comparing the effect of enoxaparin on clotting times in the HS, aPTT and TT assays, blood was drawn pre-incision with IRB approval from 12 patients scheduled for cardiac surgery. HS was assayed in the Hemochron 801 apparatus; aPTT and TT were assayed by the clinical laboratory. In the second study of the effects of heparinase digestion on enoxaparin, 6 assays were conducted on 4 different pooled plasma samples obtained commercially. Blood or plasma samples were spiked with enoxaparin to simulate "4 hr" or "12 hr" levels post- subcutaneous injection of 50 mg, which would be approximately 0.5 and 0.125 IU/ml, respectively (4). Only the low-level LMWH conditions ("12 hr") were tested for reversal by heparinase, using the manufacturer's (Dade-Behring, New Castle, DE) conditions (except we used 15 min digestion at 37 C rather than room temperature).

Results: All three assays detected the presence of enoxaparin at both simulated plasma levels (Figure). Average baseline clotting times were 232, 28.4, and 19.6 sec for HS, aPTT and TT, respectively. Of note, the average prolongation with enoxaparin for the "12 hr" level was 26.9 sec. In the reversal studies, the average decrease in clotting time with heparinase was 21.6 (11) sec, mean (SD)($p < 0.05$), which returned clotting time to 100.5 (4.7)% of the baseline values.

Conclusions: Heparinase appeared to completely reverse the anticoagulant effects of enoxaparin. In comparison with laboratory assays, the HS assay may provide a detection advantage because of the magnitude (in sec) of the decrease in clotting time with heparinase.

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