31st Annual Visiting Scholar

in Cardiothoracic Surgery

Case Presentation & Research Forum

David R. Jones, MD

Presiding

Friday, May 19, 2023
7:00 am - 12:15 pm

Visiting Scholar
David R. Jones, MD

Moderator
Kathleen Berfield, MD

Schedule of Case Presentations

7:10 am	Aldrin Alpuerto
7:15 am	Richard DuBois
7:30 am	Mad Adcox
7:45 am	Arjune Dhanekula
8:00 am	Callistus Ditah
8:15 am	James
8:30 am	James Clark
8:45am	Break

Appendix: Previous Visiting Scholars in Cardiothoracic Surgery

David R. Jones, MD

31st Annual Visiting Scholar in Cardiothoracic Surgery

May 19, 2023
Seattle, Washington

UW Medicine
DEPARTMENT OF SURGERY
DIVISION OF CARDIOTHORACIC SURGERY

Friday May 19. 2023

7:00 am - 8:45 am

Cardiothoracic Surgery Case Presentations with Discussant: David Jones, MD

9:00 am - 12:15 pm

Research Presentations with:

UW Cardiothoracic Faculty, Research Fellows, and Guest Faculty

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3:30 pm - 4:30 pm

Afternoon Lecture:

"Tumor Genomics in NSCLC: Implications for Surgically Resectable Disease."

David Jones, MD

Professor & Chief, Thoracic Surgery
Executive Vice Chair, Department of Surgery
Fiona and Stanley Druckenmiller Chair of Lung Cancer Research Department of Surgery: Memorial Sloan Kettering Cancer Center
Weill Cornell Medical College

Schedule of Research Presentations

Moderator: Farhood Farjah, MD

9:30am	Michael Mulligan	
9:35 am	Arjune Dhanekula	2-4
9:50 am	DiJon Shird	5-7
10:10 am	Kate Carroll	8-10
10:25 am	Billie Hwang	11-13
10:40 am	Nakul Thati	14-16
10:55 am	Break	
11:10 am	Gary Dong	17-19
11:25 am	Nathan Chan	20-22
11:40am	Lyubomyr Bohuta	23-24
12:00pm	Farhood Farjah	25-27
12:15 pm	End	

The Fate of the Distal Aorta Following Elective Root Replacement in Marfan Syndrome

Arjune S. Dhanekula, MD, Rachel Flodin, MS, Palca Shibale, MS, Joseph Volk, BS, Thoetphum Benyakorn, MD FRCST, Scott DeRoo, MD, Sherene Shalhub, MD, Christopher R. Burke, MD*

Objective:
Marfan syndrome (MFS) is a genetically mediated aortopathy associated with the development of aortic root aneurysm (and subsequent type A dissection) as well as type B aortic dissection (TBAD). It is unclear if the addition of a prophylactic arch operation is beneficial at the time of root replacement in MFS patients. This project aims to further understanding of the fate of the distal aorta following isolated, elective root replacement in MFS patients.

Methods:
Between 2000 and 2019, 923 patients over the age of 18 at a single academic healthcare system were identified with an administrative diagnostic coding for MFS. 379 had genetic or clinically diagnosed MFS. Of these, 182 underwent aortic root replacement, and after excluding those with acute type A dissection, the final patient cohort was 124. Serial CT scans both prior to and after elective root replacement were analyzed. The primary outcome of subsequent aortic event was defined as a composite of interval type B aortic dissection (TBAD), aneurysmal degeneration (size >4cm), and subsequent aortic intervention.

Secondary outcomes included subsequent TBAD and mortality.

Results:
A total of 124 patients (86 male (69.4%)) underwent prophylactic aortic root replacement at a mean age of 33.3 years. All patients had a clamped distal aortic anastomosis (no patients received an arch operation). Median follow-up was 11.3 years. Overall survival at 5, 10, and 15 years was 95%, 91%, and 81%, respectively. The composite primary outcome of a subsequent aortic event was noted in 30 (24.2%) patients. Patients that experienced a subsequent aortic event were more likely to be taller (192 cm vs 188 cm, $p=0.037$) and have a history of hypertension ($p=0.014$), although no difference in mortality during the follow-up period was observed between groups (33.3% vs 19.1%, $p=0.133$). 24 patients (19.5%) suffered subsequent TBAD following elective root replacement. Presence of TBAD was associated with increased mortality during the follow-up period (36.7% vs 18.1%, $p=0.045$). Rate of change in descending thoracic aortic diameter was significantly higher in the TBAD group vs no TBAD (Figure 1, $p<0.001$). Factors associated with TBAD development on multivariate logistic regression analysis included pre-operative hypertension (odds ratio (OR) 3.15, $p<0.05$) and Bentall root replacement (versus valve-sparing) (OR 2.54, $p<0.10$)..

Conclusions:
In the absence of TBAD, the distal aorta appears remarkably stable in MFS patients following isolated

elective root replacement without prophylactic arch operation. Development of TBAD occurred in nearly one-fifth of patients in this series and was associated with significantly increased mortality and aortic degeneration. Factors associated with TBAD development included a history of hypertension, likely underscoring the importance of strict lifelong blood pressure control in these patients. In MFS patients undergoing elective root replacement, future aortic morbidity seems to be driven by development of TBAD.

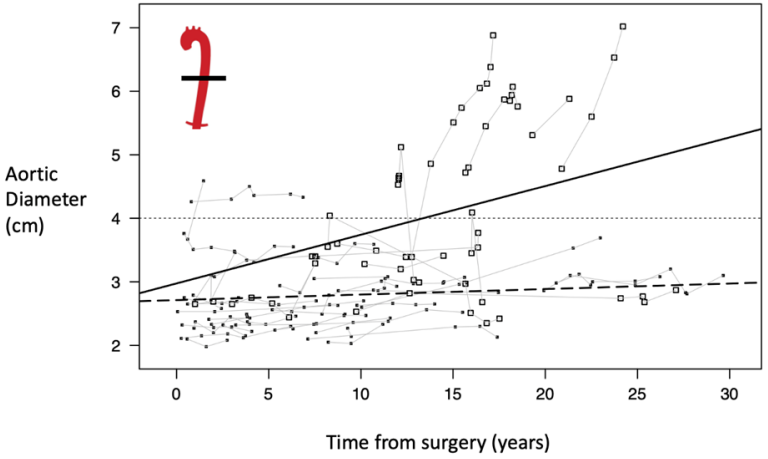

Figure 1. Changes in diameter at mid descending thoracic aorta over time comparing patients with type B dissection (solid line) and without type B dissection (dashed line) (0.077 versus 0.009, $p < 0.001$).

Cardiovascular Death Leading Cause of Mechanical Aortic Valve Replacement Mortality

DiJon Shird, MPH, Arjune Dhanekula, MD, Scott DeRoo, MD, Rachel Flodin, MS, Kenton S. Stephens, BS, Dominique DeGraff, BS, Denzel McCray, BS, Joseph Yolk, BS, Christopher R. Burke, MD.

Background:
Mechanical aortic valves are the current standard in young patients with aortic disease due to its durability and long-term efficacy. Previous studies regarding mortality after mechanical aortic valve replacement have indicated shorter life expectancy relative to the general population. However, the causes for this remain largely unknown. Thus, we seek to examine causes of death in young patients that have undergone mechanical aortic valve placement.

Methods:
Data was collected from electronic health records of patients under the age of 65 that received a mechanical aortic valve replacement at a single academic healthcare system, between the years of 2000 and 2022. These health records were also used to gather peri-operative and long-term outcomes. Exclusion criteria included emergent procedures, concomitant root replacement, and loss to follow-up or death within one year of operative date. Patient follow-up, survival status and cause of death were determined by utilizing electronic health records, a

statewide death database record, and direct patient phone calls. The final cohort consisted of 222 patients.

Results:

Of the 222-patient cohort, 155 (69.8%) were male and the average age was 53.5 by date of surgery. Within 30 days post-procedure, 47 (21.2%) of patients experienced A-fib, 9 (4.1%) required a pacemaker, 4 (1.8%) had a permanent CVA and 2 (0.9%) had experienced renal failure requiring dialysis. Over the course of the study, 26 (11.8%) suffered a massive hemorrhage, 7 (3.2%) experienced an intracranial bleed, 18 (8.18%) experienced a GI bleed and 10 (4.5%) required a re-operation on their mAVR. 40 (18%) patients were confirmed dead during the follow-up period, with cardiac-related mortality being the most common cause (50%). Overall survival at 5, 10 and 15 years was 92%, 85% and 71%, respectively. Valve size ($p=0.2$) and age of patient at time of mAVR placement ($p=0.4$) were not significant. Patients who died were more likely to be smokers, have a trileaflet aortic valve, have higher pre-operative creatinine levels, have undergone concomitant CABG, have a higher rate of long-term hemorrhagic events, and carry pre-operative diagnoses of hypertension, myocardial infarction, heart failure, and diabetes. Multivariate logistic regression analysis suggests increased risk of long-term mortality for heart failure (odds ratio (OR) 3.89, $p<0.001$), presence of native trileaflet aortic valve (OR 3.03, $p<0.05$), and massive hemorrhage in the long-term (OR 5.51, $p<0.05$).

Discussion:

This study suggests that anticoagulation plays a role in cardiovascular death in young patients with mechanical aortic valves. Within 15 years, nearly half of these patients experienced death, reintervention, or a major hemorrhagic event. Mortality did not seem to be impacted by age at time of procedure or by aortic valve size. Nearly 50% of deaths are due to cardiovascular disease, largely due to hemorrhagic events and other known cardiac risk factors (diabetes, hypertension, smoking). Thus, while anticoagulation therapy is a life-long requirement for patients with a mechanical

Ischemic Stroke Protein Signature Discovery in Novel Cardiac Surgery Patient Model

1. Kate T Carroll MD1, Emma Federico BS1, Patrick Fillingham PhD1, Dominic Nistal MD1, Guilherme Barros MD1, R. Michael Meyer MD1, Alexandra Gonzalez BS1, Malia McAvoy MD1, Jade Keen BS1, Do Lim BS1, Grant E. O'Keefe MD1, 2, Michael J. MacCoss PhD4, Christine C. Wu PhD4, Theo K. Bammler PhD5, James W. MacDonald PhD5, Andrew N. Hoofnagle MD PhD6, Stephanie H. Chen MD1, Michael R. Levitt MD1, 7, 8, 9, Christopher R. Burke MD3

2. Departments of 1Neurological Surgery, 2General Surgery, 3Cardiothoracic Surgery, 4Genomic Sciences, 5Environmental & Occupational Health Sciences, 6Laboratory Medicine & Pathology, 7Radiology, 8Mechanical Engineering, 9Stroke & Applied Neuroscience Center; University of Washington, Seattle, WA, USA

Background:
Cerebral ischemia is a known and accepted risk of deep hypothermic circulatory arrest (DHCA) in cardiothoracic surgery. While usually asymptomatic, embolic infarcts are frequently seen on surveillance imaging. Treatment of ischemic stroke depends on prompt diagnosis and there is significant ongoing research into blood-based biomarkers of stroke. The cardiothoracic surgery population presents a unique opportunity to use within-patient comparisons to identify an ischemic stroke protein signature.

Methods:
Twenty patients undergoing aortic arch repair with DHCA (n=17) or coronary artery bypass graft (n=3) have been enrolled. Blood and urine samples were taken before, during, and after surgery. Magnetic resonance imaging (MRI) of the brain was obtained within 72 hours of surgery. Infarct volume was segmented using 3D Slicer. Two techniques for proteomic analysis were used. First, plasma samples were sent for Olink Target 96 (Olink Proteomics, Uppsala, Sweden) processing using the cardiometabolic and inflammation panels. Benjami-Hochberg linear step-up analysis was used to identify proteins with significant changes and logistic regression and principal component analysis (PCA) were used to analyze proteins associated with infarct and ischemic volume. Second, samples were analyzed with a novel protein enrichment and mass spectrometry analysis technique (MAG-Net) for unbiased extracellular vesicular proteomic analysis. Analysis of variance (ANOVA) with a false discovery rate of > 0.05 was used to identify proteins with a significant change in concentration.

Results:
Post-surgical radiographic infarct occurred in 15 patients (75%), with a median volume of 108mm3. Two of the patients had new focal neurologic deficits. Linear regression of the targeted Olink proteomic data identified 11 proteins that were significantly correlated with infarct. PCA using these proteins yielded two principal components with significant correlations with infarct volume. A logistic regression

using the two significant principal components allows for binary prediction of the presence of infarct with an AUC of 0.95. Using the MAG-Net data, there was a significant change in the pre- and postoperative concentration of 261 proteins unique to patients with infarcts. Analysis of enrichment pathways of the 261 proteins in the infarct group revealed many known stroke pathways (interleukins, FAS, complement, etc).

Discussion:
Comparing protein concentrations before and after cardiothoracic surgery allows for identification of proteins whose relative concentration changes are significantly associated with neuronal death. We have employed both targeted protein analysis and unbiased protein signature discovery techniques to characterize the data and the results demonstrate feasibility of the model.

Novel Role for Extracellular Vesicles (EVs) in Redefining Lung Transplant Immunology

Billanna Hwang MPH DHSc, Rachel Waworuntu BS, An Tran BS, and Michael S. Mulligan MD
University of Washington/Department of Surgery/Cardiothoracic Division

Background:

Lung transplantation improves survival and quality-of-life for patients with end-stage lung disease. Clinical risk factors post-transplant including primary graft dysfunction (PGD) and acute and chronic lung allograft dysfunction (ALAD and CLAD) negatively impact the long-term benefits of transplantation and continues to be an area of research that has not been fully understood. Exosome immunology is a novel area of research that directly implicates extracellular vesicles (30-150nm) in playing a major role in a wide variety of diseases and immune responses. Despite the explosion of exosome studies in the last 5 years, their role in solid organ transplantation has been limited. In these studies, we aim to understand the role of exosomes in the donor: host immune responses and as prognostic biomarkers in clinical outcomes post-transplant including the development of acute and chronic rejection. In addition, we aim to develop a potentially novel paradigm that redefines lung transplant immunology through an EV lens.

Methods:

Previously stored serum serially collected from recipients post lung transplant between 2008-2016 were thawed and EVs isolated using a protocol developed in our lab. EVs were assessed for surface phenotypes associated with macrophages, T cells, and macrophage origin using a novel flow cytometry method developed in the lab. Clinical data was extracted for each patient and adjudicated for CLAD. In addition, in vivo studies were performed using isolated patient EVs to understand the functional role of EVs and the development of CLAD.

Results:

Our data shows a significant correlation between specific EV subsets and the development of CLAD in various patient populations early post-transplant. In addition, we identified populations of alveolar and interstitial macrophages-derived EVs in circulation in these patients. In vivo studies investigating the functional role of EV in CLAD development show histopathological changes in the lung associated with rejection. These data show exciting EV-based mechanisms as a possible facilitator for the development of CLAD.

Discussion:

In our studies, we have identified a few areas where EVs play a significant role in the immune responses in patients after lung transplantation. In these discovery studies, EVs are directly correlative to clinical outcomes including the development of CLAD, making them novel prognostic biomarkers. Preliminary assessment of the functional role of EVs

in vivo demonstrated a novel finding that EVs cargo from patients with CLAD suggested a significant role in the development of rejection. In addition, identification of circulating alveolar and interstitial macrophage-derived EVs post-transplant elucidates a potential key role in the donor: host response that drives alloresponse mechanisms. These studies are novel and the first in the area of lung transplantation. These findings could further our understanding of the immune complexities associated with lung transplantation resulting in better treatment options, development of therapeutics, and redefining lung transplant immunology..

The Role of Extracellular Vesicles (EVs) After Immunosuppression – Implications in Lung Transplantation

1. Nakul Thati BS, Billanna Hwang, MPH DHSc, Rachel Waworuntu BS, An Tran BS,
and Michael S. Mulligan, MD

2. University of Washington/Department of Surgery/Cardiothoracic Division

Background:
Immunosuppression is a key component in the successful outcomes for patients after lung transplantation. Despite the advances in new classes of immunosuppressive agents and evolving cocktails of IS used for maintenance, there still remains long-term complications including nephrotoxicity and malignancy. In addition, the role of IS in protecting the donor graft without long-terms effects continues to be unachievable with the development of and limit overall transplant survival including the development of chronic lung allograft dysfunction (CLAD). Host cells exposed to IS post-transplant have different profiles including secretory components such as cytokines, chemokines, and EVs. EVs are a novel class of "cellular garbage" that is secreted from the cell and is involved in a number of immune responses including activation, polarization, and alloresponses. The use of IS is an important part of maintenance after transplant, but the impact on the host immune system including the development of CLAD still largely remains limited and unknown. In

these studies, we investigate the potential impacts of IS on the host immune system through a novel lens of EVs. Better understanding of IS-mediated EV immune evasion is needed to potentially predict patient immune responses and improve the use of IS post-transplant that facilitates better long term graft outcomes and mitigates the development of CLAD.

Methods:
In vitro EL4 cultures were treated with varying concentrations (1nM, 10nM, 100nM) of either cyclosporine A, MMF, or rapamycin. Cells were counted to determine suppressive capabilities. EVs were isolated from culture supernatant collected after 72 hours and analyzed by Exo-Flow (protocol developed in our lab) for T cell surface markers including Tregs. ELISA were performed on culture supernatant and assessed for IL1Bβ, IL4, IL6, IL8, INFγ, and TNFα levels. Secondary cultures of EL4 (untreated with IS) were co-cultured with EVs derived from cells treated with IS and similar assays performed as previously described.

Results:
Our data shows that EVs derived from cells treated with IS are suppressive and can be transferred to naïve cultures. EVs isolated from various IS treated cells show different T cell surface markers and cytokine profiles when compared to controls.

Discussion:
In these novel studies, we show for the first time the ability of EVs to independently suppress proliferation

in vitro. EVs-derived from either CSP, MMF, or Rapamycin treated cells show remarkable differences in T cell surface markers and secreted cytokines. These exciting new data could possibly shed new light into EV-based mechanisms for different courses of IS that affect the host immune responses long term and ultimately the longevity of the allograft. In addition, this exciting new area of research could also elucidate the role of IS-derived EVs on the development of CLAD.

Extracellular Vesicles (EVs) and Primary Graft Dysfunction (PGD) Post Lung Transplantation: A Preliminary Study

Gary Dong BS1, Billanna Hwang MPH DHSc1, Rachel Waworuntu BS1, An Tran BS1, Pablo Sanchez MD2, and Michael S. Mulligan MD1

1. University of Washington/Department of Surgery/Cardiothoracic Division

2. University of Pittsburg/Department of Surgery/Cardiothoracic Division

Background:
Primary graft dysfunction (PGD) is a clinical syndrome of lung injury shortly after transplant and can have detrimental effects on long term survival of the graft. High grade PGD has significantly poorer outcomes and includes lung edema, altered pulmonary compliance, reduced gas exchange and circulation. While clinical risk factors associated with PGD have been extensively studied, the mechanisms and pathophysiology have not. Additionally, numerous studies have try to identify molecular biomarkers that predict the onset, but have not been successful. A major source for potential biomarkers that has not yet been extensively explored are EVs. EVs are vesicles secreted by a parent cell that are functionally capable of influencing a variety of immune responses. In these studies, we aim to identify specific EVs that correlate to the development of PGD.

Methods:
Serum was serially collected from lung transplant recipients at the University of Pittsburg at times 0, 24, 48, 72 hours, and 7 days post-transplant. Serum samples were thawed and EVs isolated using a protocol developed in our lab and assessed for size using a Nanosight. EVs were assessed for surface phenotypes associated with macrophages, T cells, and macrophage origin using a novel flow cytometry. Degree of PGD was assessed for each patient by at the University of Pittsburg at T24 and T72. Preliminary statistical analysis was performed using GraphPad comparing EV profiles, grade of PGD, and days after transplant.

Results:
In these studies, we are able to show various EV surface phenotypes correlating to degree of PGD at certain times post-transplant. CD68 showed no significance at any time points while CD86+ EVs showed statistical significance at D0, 1, 2, and 7 comparing PGD grade 0 vs. 3. CD163+ EVs showed potential significance comparing grade 0 vs. 3 and 1 vs. 3 on day 1 post-transplant. No macrophage EV markers were significant for T24-0/T72-0 vs. T24-3/T72-3. Macrophage subsets showed significance in circulating CD14+ EVs.

Discussion:

In these preliminary studies, we have identified EVs that could play a significant role in the development of PGD in patients after lung transplantation and it appears to be directly correlative to grade of PGD. These are novel findings and will move the field forward in understanding immune responses that manifest into clinical complications associated with PGD. By taking a multilevel, translational approach, it will further our understanding of all complications associated with PGD and role in acute lung failure after transplant will provide much need insight into better treatment strategies. These data provides another piece to the overall immunology puzzle that is lung transplantation and will provide novel insight into host: donor:EV paradigm.

Phenotyping and Immune Signaling of Monocytes and Macrophages in Porous Precision Templated Scaffolds

Nathan R. Chan[1, 2], Billanna Hwang[3], Michael S. Mulligan[3], James D. Bryers[1, 2]

1. Molecular Engineering and Sciences Institute, University of Washington, Seattle, WA, 98195, USA
2. Department of Bioengineering, University of Washington, Seattle, WA, 98195, USA
3. Department of Surgery, University of Washington, Seattle, WA, 98195, USA

Background:
Porous precision templated scaffolds (PTS) are three-dimensional biomaterial constructs where the pore size and pore interconnects can be precisely controlled, allowing for the creation of scaffolds with tunable characteristics and implant outcomes. Regardless of the polymer used in construction and without the use of any signaling/stimulating molecules, PTS with uniform, interconnected, 40 μm pores have shown a remarkable ability in immunomodulating resident cells for tissue regeneration. In contrast, PTS with smaller or larger pores result in a pro-inflammatory and pro-fibrotic foreign body response. The mechanism behind the pore-size-mediated phenomenon remains unclear; however, monocyte and macrophage phenotype have been identified as key mediators in regulating implant outcome within the PTS. Here, we quantify the infiltration kinetics and functional role of

circulating monocytes to subcutaneously implanted PTS. We then identify the regulatory role of MyD88-dependent signaling downstream of Toll-like receptors (TLRs) that drive the regenerative, pro-healing response in 40 μm PTS.

Methods: Poly(2-hydroxyethyl methacrylate) (pHEMA) scaffolds were fabricated using a patented sphere-templating method to create uniformly distributed pores and interconnects throughout the scaffold. To determine the role of circulating monocytes, 40 μm PTS (healing) or 100 μm PTS (non-healing) were subcutaneously implanted in a fluorescently-labeled myeloid reporter mouse line (LysM-Cre:mTmG) and explanted at 3, 5, and 7 days post-implantation. Circulating monocytes were depleted by intravenous injection of clodronate liposomes. Cells recovered from explanted PTS were analyzed by flow cytometry, ELISA, RT-qPCR, histology, and scanning electron microscopy (SEM). To elucidate the role of MyD88-dependent wound healing, 40 μm PTS were subcutaneously implanted in MyD88KO mice and compared to 40 μm and 100 μm PTS implanted in LysM-Cre:mTmG mice at 1 and 2 weeks post-implantation. Phenotyping was performed by immunofluorescence staining on scaffold-resident cells expressing CD3 (T lymphocytes) CD86 (M1-like macrophages), CD163 (M2-like macrophages), or CD206 (M2-like macrophages). Stained scaffolds were analyzed by HALO® using a CytoNuclear FL algorithm to quantify the total number of cells expressing each surface marker.

Results/Discussion: 40 μm PTS contained a greater infiltration of myeloid cells while a greater proportion of pro-inflammatory Ly6Chigh monocytes infiltrated into the 100 μm PTS. When 40 μm PTS were implanted in monocyte-depleted mice, trichrome staining showed a collagen-rich foreign body capsule at the implant surface and extensive pore-spanning cellular networks similar to 100 μm PTS in untreated mice. Additionally, high-magnification SEM images confirmed the presence of a fibrous cellular structure and a large amount of ECM protein deposits adherent to the pore surface compared to 40 μm PTS implanted in untreated mice. As a function of pore size, 40 μm PTS exhibited a pro-healing CD206+ phenotype while 100 μm PTS demonstrated a pro-inflammatory CD86+ phenotype. Using a MyD88KO mouse model, we found that MyD88 signaling was involved in the pro-healing mechanisms seen in 40 μm PTS through a decrease in CD206 expression. Overall, these findings further our understanding of the molecular mechanisms underlying cell behavior and tissue regeneration in PTS and implantable biomaterials.

Bloodless Norwood is Possible: Encouraging Results of Blood Conservation in Neonatal Open-Heart Surgery.

Lyubomyr Bohuta MD, PhD,a Kevin Charette CCP,b Titus Chan MD, MS, MPP,c Denise Joffe MD, d Andrew Koth MD, c Christina L. Greene MD,a David Mauchley MD, a D. Michael McMullan MDa

1. From the Divisions of aCardiac Surgery, cCritical Care, dAnesthesia and bPerfusion services, Seattle Children's Hospital, WA

Objective: To report early outcomes of blood conservation in neonatal open-heart surgery.

Methods:
Ninety-nine patients undergoing neonatal open-heart surgery during the implementation of a blood conservation program between May 2021 and February 2023 were reviewed. Patients either received traditional blood management (Blood Prime (BP), n=43) or received blood conservation strategies (Clear Prime (CP), n=56). Baseline characteristics and outcomes were compared between groups.

Results:
There was no difference in body weight (median 3.2 kg vs. 3.3 kg, p=0.83), age at surgery (median 5 days vs. 5 days, p=0.37), distribution of STAT categories or duration of cardiopulmonary bypass. Patients in the CP group had higher preoperative hematocrit (Hct) (median 41% vs. 38%, p<0.01), shorter postoperative

mechanical ventilation time (median 48 hrs. vs. 92 hrs., p=0.02) and postoperative ICU length of stay (median 6 days, vs. 9 days, p<0.01) than patients in the BP group. Fourteen patients (25%) in the CP group, including 1 Norwood patient, were discharged without any transfusion. Among patients within the CP group, hospitalizations without blood exposure were associated with higher preoperative Hct (median 43% vs. 40%, p=0.02), shorter postoperative mechanical ventilation times (median 22 hrs. vs. 66 hrs., p=0.01) and shorter postoperative hospital stays (median 10 days vs. 15 days, p=0.02). were independently associated with an increased risk of surgical reintervention or mortality.

Conclusions:
Bloodless surgery is possible in a significant proportion of neonates undergoing open-heart surgery, including the Norwood operation, even in the early stages of experience. Early clinical results are favorable but long-term follow-up and continued efforts are warranted to prove safety and reproducibility.

The Volume Pledge is Not Associated with Better Short-Term Outcomes After Lung Cancer Resection

Farhood Farjah, MD, MPH, FACS1; Maria V. Grau-Sepulveda, MD2; Henning Gaissert, MD3; Mark Block, MD4; Eric Grogan, MD, MPH, FACS5; Lisa M. Brown, MD, MAS, FACS6; Andrzej S. Kosinski, PhD2,7; and Benjamin D. Kozower, MD, MPH8

1Department of Surgery, University of Washington, Seattle, WA
2Duke Clinical Research Institute, Durham, NC
3Division of Thoracic Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA
4Division of Thoracic Surgery, Memorial Healthcare System, Hollywood, FL
5Department of Thoracic Surgery, Vanderbilt University Medical Center, Nashville, TN
6Section of General Thoracic Surgery, Department of Surgery, University of California Davis Health, Sacramento, CA
7Department of Biostatistics and Bioinformatics, Duke University, Durham, NC
8Department of Surgery, Washington University School of Medicine, St. Louis, MO

Background:
We examined the relationship between short-term outcomes and hospitals and surgeons who met minimum volume thresholds for lung cancer resection based on definitions provided by the Volume Pledge. A secondary aim was to evaluate the volume-outcome relationship to determine

alternative thresholds in the event the Volume Pledge was not associated with outcomes.

Methods:
We conducted a retrospective study (2015-2017) using the Society of Thoracic Surgeons General Thoracic Surgery Database. We used generalized estimating equations that accounted for confounding and clustering to compare outcomes across hospitals and surgeons who did and did not meet the Volume Pledge criteria: ≥40 patients per year for hospitals and ≥20 patients per year for surgeons. Our secondary aim was to model volume by using restricted cubic splines to determine the association between volume and short-term outcomes.

Results:
Among 32,183 patients, 465 surgeons, and 209 hospitals, 16,630 patients (52%) received care from both a hospital and surgeon meeting the Volume Pledge criteria. After adjustment, there was no relationship with operative mortality, complications, major morbidity, a major morbidity-mortality composite end point, or failure to rescue. The Volume Pledge group had a 0.5 day (95% CI, 0.2 to 0.7 day) shorter length of stay. Our secondary aim revealed a nonlinear relationship between hospital volume and complications in which intermediate-volume hospitals had the highest risk of complications. Surgeon volume was associated with major morbidity, a major morbidity-mortality composite end point, and length of stay in an inverse linear

fashion. Only 8% of surgeons had volumes associated with better outcomes.

Discussion:
The Volume Pledge was not associated with better outcomes except for a marginally shorter length of stay. A re-examination of volume-outcome relationships for hospitals and surgeons yielded mixed results that did not reveal a practical alternative for volume-based quality improvement efforts.

Appendix

University of Washington
Visiting Scholars in Cardiothoracic Surgery

1992		Tirone E. David, MD Head, Division of Cardiovascular Surgery The Toronto Hospitals
1993		Hermes C. Grillo, MD Professor of Surgery, Harvard Medical School Chief, General Thoracic Surgery Massachusetts General Hospital
1994		Andrew S. Wechsler, MD Professor and Chairman, Department of Surgery Medical College of Virginia Virginia Commonwealth University
1995		Hillel Laks, MD Professor and Chief, Cardiothoracic Surgery UCLA Medical Center
1996		James L. Cox, MD Cardiothoracic Surgeon in Chief Barnes-Jewish Hospital Vice-Chairman, Dept. of Surgery Washington University School of Medicine
1997		D. Craig Miller, MD Professor of Cardiovascular Surgery Stanford University School of Medicine

1998		Mark B. Orringer, MD Professor and Chief of the Section of Thoracic Surgery University of Michigan
1999		Lawrence H. Cohn, MD Professor Surgery Harvard Medical School Brigham and Women's Hospital/Children's Hospital
2000		Richard A. Jonas, MD Cardiovascular Surgeon-Chief Children's Hospital, Boston, Massachusetts Harvard Medical School
2001		G. Alexander Patterson, MD Joseph C. Bancroft Professor, Division of Cardiothoracic Surgery Department of Surgery at Washington University
2002		Irving L. Kron, MD Chief, Division of Thoracic and Cardiovascular University of Virginia School of Medicine
2003		Vaughn A. Starnes, MD Chairman, Department of Cardiothoracic Surgery University of Southern California
2004		Douglas J. Mathisen, MD Hermes C. Grillo Professor in Thoracic Surgery Chief, Cardiothoracic Surgery Massachusetts General Hospital

2005		William A. Baumgartner, MD Vice Dean for Clinical Affairs President of the Clinical Practice Associations John Hopkins Medicine and Hospital

2006		Martin Elliott, MD Chairman of Cardiothoracic Surgery Great Ormond Street Hospital for Children NHS Trust London, United Kingdom
2007		Larry R. Kaiser, MD The John Rhea Barton Professor Chairman of the Department of Surgery University of Pennsylvania
2008		David A. Fullerton, MD Head, Division of Cardiothoracic Surgery University of Colorado Health Sciences Center
2009		Edward L. Bove, MD Helen and Marvin Kirsch Professor of Surgery, Director, Pediatric Cardiovascular Surgery University of Michigan
2010		Valerie W. Rusch, MD Chief of Thoracic Surgery William G. Cahan Chair of Surgery Memorial Sloan-Kettering Cancer Center
2011		Thoralf M. Sundt, III, MD Chief of Cardiac Surgery Massachusetts General Hospital

2012		Pedro del Nido, MD Chief of Cardiac Surgery Boston Children's Hospital
2013		Shaf Keshavjee, MD Director, Toronto Lung Transplant Program Surgeon in Chief, University Health Network University of Toronto
2014		Bruce Lytle, MD Chairman, Heart and Vascular Institute, Cleveland Clinic
2015		Frank Hanley, MD Lawrence Crowley, MD Endowed Professorship in Child Health, Stanford University
2016		Keith Nauheim, MD The Vallee L. and Melba William Professor Chief of Cardiothoracic Surgery Saint Louis University
2017		Michael Mack, MD Medical Director of Cardiovascular Surgery Chairman of the Heart Hospital Baylor Plano Baylor Health Care System

2018		Joseph A. Dearani, MD Professor of Surgery Chairman of the Department of Cardiovascular Surgery Mayo Clinic College of Medicine and Science
2019		Sean C. Grondin, MD, MPH Professor of Surgery Head, Department of Surgery Cumming School of Medicine, University of Calgary, Calgary Zone Clinical Department Head Alberta Health Services
2021		Joseph E. Bavaria, MD Vice Chief, Division of Cardiovascular Surgery Director, Thoracic Aortic Surgery Program Co-Director, Transcatheter Valve Program Brooke Roberts - William Maul Measey Professor in Surgery
2022		Christopher A. Caldarone, MD Donovan Chair and Chief Congenital Heart Surgery, Texas Children's Hospital Professor of Surgery, Baylor College of Medicine
2023		David R. Jones Professor & Chief, Thoracic Surgery Executive Vice Chair, Department of Surgery Fiona and Stanley Druckenmiller Chair of Lung Cancer Research Department of Surgery: Memorial Sloan Kettering Cancer Center Weill Cornell Medical College

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