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Normothermic Ex Vivo Lung Perfusion (Novel) as an Assessment of Extended Criteria Donor Lungs: A Prospective Multi-Center Clinical Trial

P. G. Sanchez

E. G. Chan

R. D. Davis

M. Hartwig

T. Machuca

See next page for additional authors

Authors

P. G. Sanchez, E. G. Chan, R. D. Davis, M. Hartwig, T. Machuca, B. Whitson, M. Daneshmand, F. D. Ovidio, J. Dcunha, M. Weyant, M. Jessen, C. Bermudez, M. Mulligan, T. Wozniak, W. Lynch, Hassan Nemeh, C. Caldeira, T. Song, D. Kreisel, P. Camp, D. Ramzy, B. Griffith, and E. Cantu

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Transcriptomic Analysis of Right Ventricular Adaptation and Failure in a Novel Ovine Model of Pulmonary Hypertension

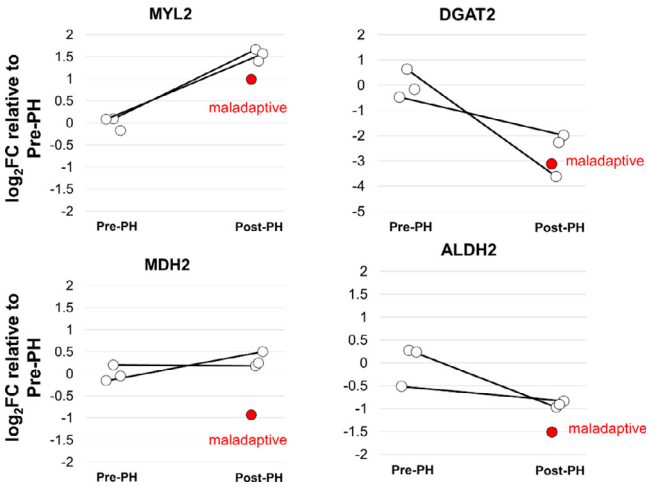
R. Ukita,[1] W.K. Wu,[1] J.W. Stokes,[1] V. Agrawal,[1] Y. Patel,[1] J.R. Talackine,[1] N. Cardwell,[1] C. Demarest,[1] Y. Tipograf,[1] E.J. Tsai,[2] E. Carrier,[1] A. Hemnes,[1] E.B. Rosenzweig,[2] K. Cook,[3] M. Bacchetta,[1] and J. West.[1] [1]Vanderbilt University Medical Center, Nashville, TN; [2]Columbia University Medical Center, New York, NY; and the [3]Carnegie Mellon University, Pittsburgh, PA.

Purpose: Right ventricular failure (RVF) is a large contributor to morbidity and mortality in pulmonary hypertension (PH). Molecular understanding of RVF may facilitate identification of novel drug and device therapy targets. Using our previously published large animal model of PH-RVF, we performed RNA-seq analysis of RV tissues sampled from healthy sheep, PH sheep, and PH sheep that received mechanical circulatory support (MCS).

Methods: We assessed RV gene expression in adult sheep prior to and after completion of a previously described PH model. Three PH sheep subsequently underwent acute MCS for 3-6 hours. Right ventricular (RV) free wall tissues were collected prior to PA banding and at termination of MCS (pre-PH vs post-PH, N=3 each). One subject experienced severe maladaptive RVF and expired prior to MCS. This maladaptive characterization was based on its mixed venous saturation below 30% and several liters of ascites and pleural effusion found at necropsy. The pre-PH and post-PH RV tissue samples were analyzed for gene expression profile with RNAseq and studied with over-representation analysis to elucidate enriched pathways.

Results: RNAseq identified 358 genes with differential expression between pre-PH and post-PH tissue samples ($p < 0.01$, >2-fold change). Enrichment analysis showed that these genes were related to cardiomyocyte muscularization and proliferation, indicating adaptation to RV loading. The maladaptive RV sample, even when compared to the other PH sheep that received MCS, demonstrated markedly reduced expression of metabolic genes, especially in fatty acid oxidation.

Conclusion: RV load stress coincides with differential expression of genes related to cardiomyocyte muscularization and proliferation. Observations of reduced expression of fatty acid oxidation genes in a maladaptive subject with RVF warrants further investigation. The role of mechanical support on RV gene expression needs to be further studied in longer-term settings.



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Sex Differences in Endothelial-to-Mesenchymal Transition in Chronic Thromboembolic Pulmonary Hypertension

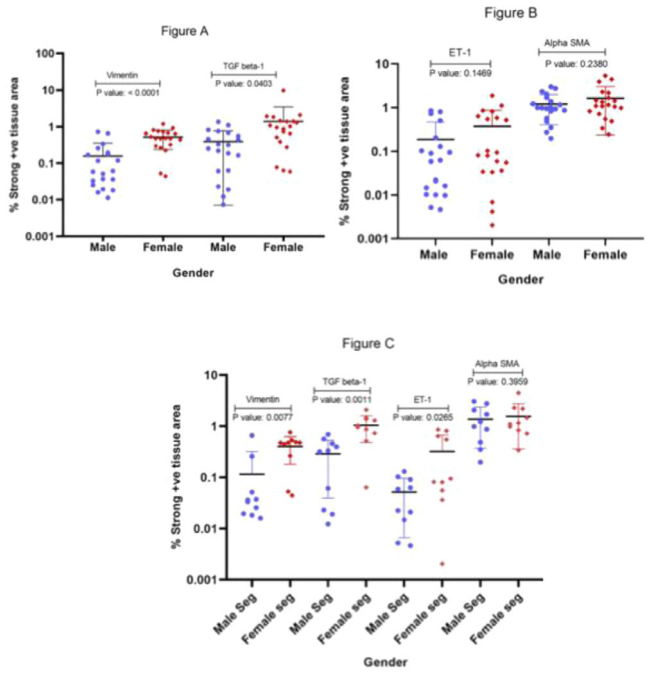
U. Asghar,[1] J. Man,[2] L. Wu,[1] and M.D. Perrot.[2] [1]Latner Thoracic Surgery Research Laboratories, Toronto General Hospital Research Institute, Toronto, ON, Canada; and the [2]Division of Thoracic Surgery, Toronto General Hospital, Toronto, ON, Canada.

Purpose: Chronic Thromboembolic Pulmonary Hypertension (CTEPH) results from thrombus organization and obstruction of pulmonary arteries. Population studies suggest sex differences in outcomes. Yet, the mechanisms contributing to sex differences in CTEPH remain poorly understood. We propose that endothelial cells present in the organized thrombi undergo endothelial-to-mesenchymal transition (EndoMT); a process in which endothelial cells lose polarity, cell-to-cell contacts, and gradually adopt mesenchymal cells characteristics. Here, we find that markers of EndoMT are significantly higher in female vs male patients, which could contribute to sex differences in CTEPH pathophysiology.

Methods: A retrospective cohort of ten male and ten female CTEPH patients was studied. Pulmonary endarterectomy specimens from these patients were separated into lobar and segmental sections. Two samples (lobar and segmental) from each patient were paraffin embedded and used for Immunohistochemistry (IHC) analysis. IHC staining for markers for EndoMT, including endothelin-1 (ET-1), Transforming growth factor beta-1 (TGF beta-1), vimentin and alpha smooth muscle cell actin (alpha SMA), was performed. Quantitative tissue area analysis for each marker was performed using the HALO image analysis platform.

Results: We found that females have significantly higher total expression of vimentin and TGF beta-1 (Figure A). There was a trend towards increased total expression of ET-1 and alpha SMA in females that is not significantly different from males (Figure B). However, we found that female segmental sections have higher expression levels for vimentin, TGF beta-1, ET-1 and alpha SMA than male segmental sections (Figure C).

Conclusion: Increased expression of EndoMT markers may account for sex differences in the pathophysiology and outcomes of CTEPH. We will validate these findings and further explore EndoMT in the pathogenesis of CTEPH.



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Normothermic *Ex Vivo* Lung Perfusion (Novel) as an Assessment of Extended Criteria Donor Lungs: A Prospective Multi-Center Clinical Trial

P.G. Sanchez,[1] E.G. Chan,[2] R.D. Davis,[3] M. Hartwig,[4] T. Machuca,[5] B. Whitson,[6] M. Daneshmand,[7] F. D Ovidio,[8] J. DCunha,[9] M. Weyant,[10] M.

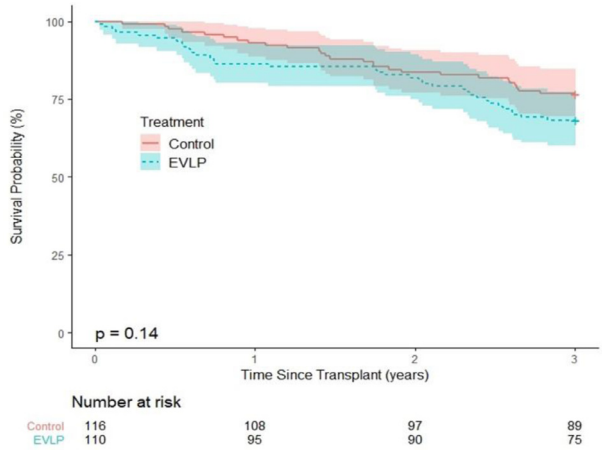
Jessen,[11] C. Bermudez,[12] M. Mulligan,[13] T. Wozniak,[14] W. Lynch,[15] H. Nemeh,[16] C. Caldeira,[17] T. Song,[18] D. Kreisel,[19] P. Camp,[20] D. Ramzy,[21] B. Griffith,[22] and E. Cantu.[23] [1]Cardiothoracic Surgery, University of Pittsburgh, Pittsburgh, PA; [2]University of Pittsburgh, Pittsburgh, PA; [3]Florida Hospital Transplant Center, Orlando, FL; [4]Duke University, Durham, NC; [5]University of Florida, Gainesville, FL; [6]Ohio State University, Columbus, OH; [7]Emory University, Atlanta, GA; [8]Columbia University, New York, NY; [9]Mayo Clinic, Scottsdale, AZ; [10]University of Colorado, Denver, CO; [11]University of Texas Southwestern, Dallas, TX; [12]University of Pennsylvania, Philadelphia, PA; [13]University of Washington, Seattle, WA; [14]University of Wisconsin, Madison, WI; [15]University of Michigan, Ann Harbor, MI; [16]Henry Ford Hospital, Detroit, MI; [17]Tampa General Hospital, Tampa, FL; [18]University of Chicago, Chicago, IL; [19]Washington University, Saint Louis, MO; [20]Brigham and Women's Hospital, Boston, MA; [21]Cedars-Sinai Medical Center, Los Angeles, CA; [22]University of Maryland Medical Center, Baltimore, MD; and the [23]University of Pennsylvania, Philadelphia, PA.

Purpose: *Ex vivo* lung perfusion (EVLP) allows re-evaluation of extended criteria/marginal donor lungs. This can increase the number of lung transplants. However, the long-term outcomes of transplanting EVLP-screened lungs in a multicenter setting are unknown. We proposed to evaluate the short- and long-term outcomes of EVLP performed at multiple centers.

Methods: This is a prospective, nonrandomized clinical trial. Seventeen lung transplant centers in the United States. Adult patients with end-stage pulmonary disease requiring lung transplant from May 2011 to December 2017 were eligible. Lung allografts initially deemed extended criteria/marginal (n=216) were placed on EVLP and re-evaluated prior to transplant. Patients received either standard donors (n=116) or lungs screened with EVLP (n=110).

Results: Half of the lung grafts (110/216, 50.9%) placed on EVLP were transplanted. The incidence of primary graft dysfunction 24 hours post-transplant was higher in the EVLP group (25.5% vs 10.3%, p=0.003), but was not significantly different 48 hours (EVLP: 15.5%, control: 9.5%, p=0.49) and 72 hours (13.6% vs 6.9%, p=0.34) post-transplant. Survival was not significantly different between the 2 groups 1 year (n=226, EVLP: 86%, control: 94%, p=0.06), 3 years (n=226, EVLP: 68%, control: 76%, p=0.16, Figure), or 5 years (n=159, EVLP: 59%, control: 65%, p=0.68) post-transplant. There were also no differences in pulmonary function, the incidence of chronic lung allograft dysfunction or quality of life measures post-transplant.

Conclusion: In this multicenter study, recipients of lungs that were re-evaluated on EVLP and deemed suitable for transplant had similar outcomes as a recipients of a standard lung transplants. EVLP offers the opportunity to screen donated lungs initially considered high risk and can safely increase the availability of transplantable lungs without compromising outcomes.



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Increasing Lung Transplant Availability with Normothermic Ex Vivo Lung Perfusion (EVLP) at a Dedicated Facility and a Centralized Lung Evaluation System (CLES): 3-Year Outcomes

J.M. Mallea,[1] A.W. Brown,[2] D. Johnson,[3] C. Keller,[1] M. Roberts,[4] P. Sanchez,[5] J. D'Cunha,[6] D. Erasmus,[1] and M. Hartwig.[7] [1]Mayo Clinic Florida, Jacksonville, FL; [2]INOVA, Falls Church, VA; [3]United Therapeutics Corporation, Research Triangle Park, NC; [4]Lung Bioengineering, Silver Spring, MD; [5]University of Pittsburgh, Pittsburgh, AZ; [6]Mayo Clinic Arizona, Phoenix, AZ; and the [7]Duke University Health System, Durham, NC.

Purpose: This study is the first prospective, multicenter trial to examine the safety and feasibility of a dedicated EVLP facility to evaluate lungs declined for standard transplantation in the US.

Methods: Seven transplant centers from the Midwest and Eastern US referred 105 lungs that had been rejected by standard transplant criteria to a dedicated EVLP facility (NCT02234128). Lungs were perfused and ventilated using the Toronto EVLP protocol. Following EVLP, 63 were accepted for transplantation (utilization rate of 60%). The matched control group consisted of 49 lungs transplanted without the use of EVLP. Bronchiolitis Obliterans Syndrome (BOS) was defined per protocol as airflow limitation in the absence of other etiologies and did not require histopathology documenting BOS. BOS diagnosis was graded in accordance with 2014 ISHLT guidelines as follows: forced expiratory volume in 1 second (FEV_1) 66-80% of baseline was grade 1, FEV_1 51-65% of baseline was grade 2, and FEV_1 <50% of baseline was grade 3.

Endpoints: The primary endpoints were the proportion of recipients with bronchiolitis obliterans syndrome (BOS) grade (1, 2, or 3), time to death, and mortality rate at three years post-transplant.

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Characteristics and Outcomes of Lung Transplants Performed with Ex-Vivo Lung Perfusion

Y. Xia,[1] S. Patel,[2] D. Sayah,[2] R. Biniwale,[2] and A. Ardehali.[2] [1]Surgery, Division of Cardiac Surgery, University of California Los Angeles, Los Angeles, CA; and the [2]University of California Los Angeles, Los Angeles, CA.

Purpose: Ex-vivo lung perfusion (EVLP) can be used to assess and rehabilitate donor lungs to expand the donor pool. However, the frequency of EVLP utilization and its outcomes are not well-studied. The goal of this study was to describe the characteristics and outcomes of lungs transplants performed with EVLP in the US.

Methods: We conducted retrospective review of the UNOS registry of all primary adult lung transplant recipients from Feb 28, 2018 to June 30, 2021, excluding recipients with prior transplants, multiorgan transplants, and those waitlisted for other organs. Lung transplants were dichotomized as those that were performed with EVLP versus no EVLP. Baseline characteristics and short-term outcomes were compared. One-year survival was assessed by the Kaplan Meier method and multivariable Cox proportional hazards regression.

Results: Of 8,204 lung transplants performed during our study period, 426 (5.2%) were performed with EVLP. Perfusion was performed by the OPO in 29(7%), transplant center in 291(68%), and external perfusion center in 106(25%) of cases. EVLP donors were older (39±13 vs 36±14 yrs, p<0.01), more likely DCD (31% vs 5%, p<0.01), and had lower P:F ratio (415±124 vs 442±130, p<0.01). Recipients had lower LAS scores[39(35-53) vs 41 (35-57), p<0.01)]. EVLP lungs traveled further[232(122-489) vs 169 (71-270) nautical miles, p<0.01], had longer ischemic times(11.5± 4.1 vs 5.5±1.6 hrs, p<0.01), and were more likely double lung transplants (85% vs 76%, p<0.01). At 72 hours, recipients of EVLP lungs were more likely to remain intubated(47% vs 30%, p<0.01), be on ECMO(16% vs 8%, p<0.01), and experience PGD grade III (24% vs 17%, p<0.01). They also had higher total length of stay[21(13-39) vs 18(13-30) days, p<0.01). EVLP was associated with worse one-year survival on univariable(84% vs 88%, HR 1.41, 95% CI 1.07-1.85, p=0.02) but not multivariable analysis (aHR 1.18, 95% CI 0.88-1.59, p=0.26), particularly after adjusting for DCD donation(aHR 1.46, 95% CI 1.11-1.91)