

Endothelin-1 Activation Is Associated With Post-Operative Hypoxemia in Infants with Single Ventricle Heart Disease Undergoing Superior Cavo-Pulmonary Anastomosis

Benjamin S. Frank MD¹, Karlise Lewis MS¹, Ludmila Khailova MS¹, Lori Silveira PhD², Max B. Mitchell MD³, Gareth J. Morgan MD¹, Mark Twite MD⁴, Jelena Klawitter PhD⁵, D. Dunbar Ivy MD¹, Michael V. Di Maria MD¹, Jesse A. Davidson MD, MPH¹

¹University of Colorado, Department of Pediatric Cardiology, ²University of Colorado, Department of Biostatistics, ³University of Colorado, Department of Pediatric Cardiothoracic Surgery, ⁴University of Colorado, Department of Pediatric Anesthesiology, ⁵University of Colorado, Department of Anesthesiology



Children's Hospital Colorado

Conflicts of Interest

- Benjamin Frank has documented no financial relationships to disclose or Conflicts of Interest (COIs) to resolve.



Single Ventricle Heart Disease

- Single ventricle heart disease (SVHD) includes 10% of all congenital heart defects and is universally fatal without intervention.
- Staged surgical palliation can allow survival:
 - **Stage 1 (infancy):** pulsatile pulmonary flow when resistance is high.
 - **Stage 2 (4-6 mo, SCPA):** passive pulmonary flow from SVC to PA after resistance falls.
 - **Stage 3 (2-4 yo, TCPC):** all systemic venous return must pass passively through lungs.
- SVHD patients with inadequate pulmonary blood flow clinically manifest hypoxemia.

Endothelin-1

- Endothelin-1 (ET-1) is a potent pulmonary vasoconstrictor that is inducible by both systemic inflammation and tissue hypoxia.
- Prior studies have noted an ET-1 rise in children after cardio-pulmonary bypass.
- No study has evaluated ET-1 activation or its association with hypoxemia in patients undergoing SCPA (Stage 2).

Hypothesis

- Infants undergoing Stage 2 palliation with higher serum ET-1 levels before and after surgery will have evidence of decreased pulmonary blood flow as measured by lower oxygen saturation.

Methods

- Prospective, observational cohort study of infants with SVHD undergoing Stage 2.
- SVHD case samples were collected at pre-op cath (systemic vein and pulmonary vein) and 2, 24, and 48 hours post-op (systemic vein).
- Control venous samples obtained from similar age infants undergoing non-cardiac surgery.
- Serum ET-1 concentration measured by ELISA.

Methods – Clinical Data

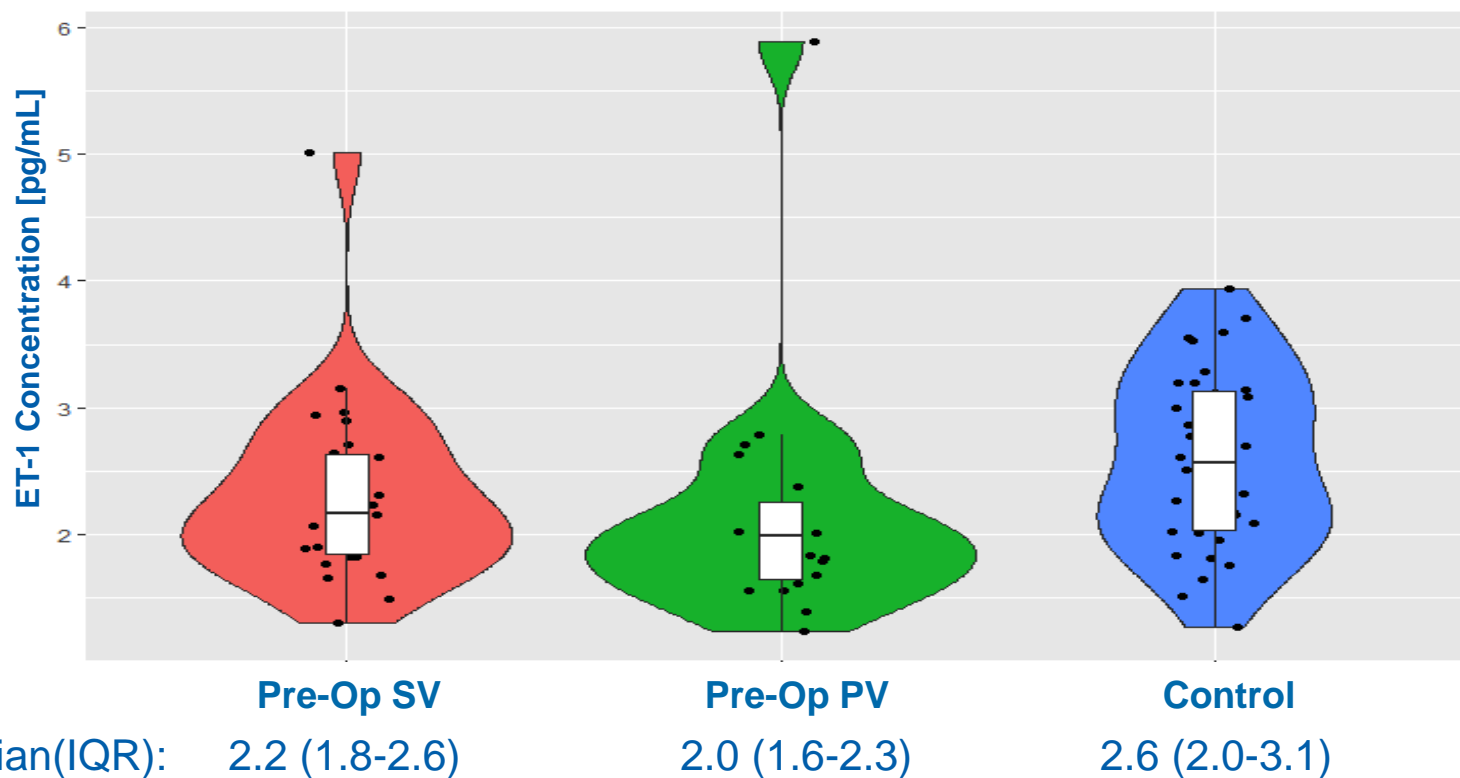
- O₂ saturation in the first 72 post-operative hours measured at one-minute intervals.
- Hypoxemia burden calculated as percent of time spent below 70% O₂ saturation.

Study Population

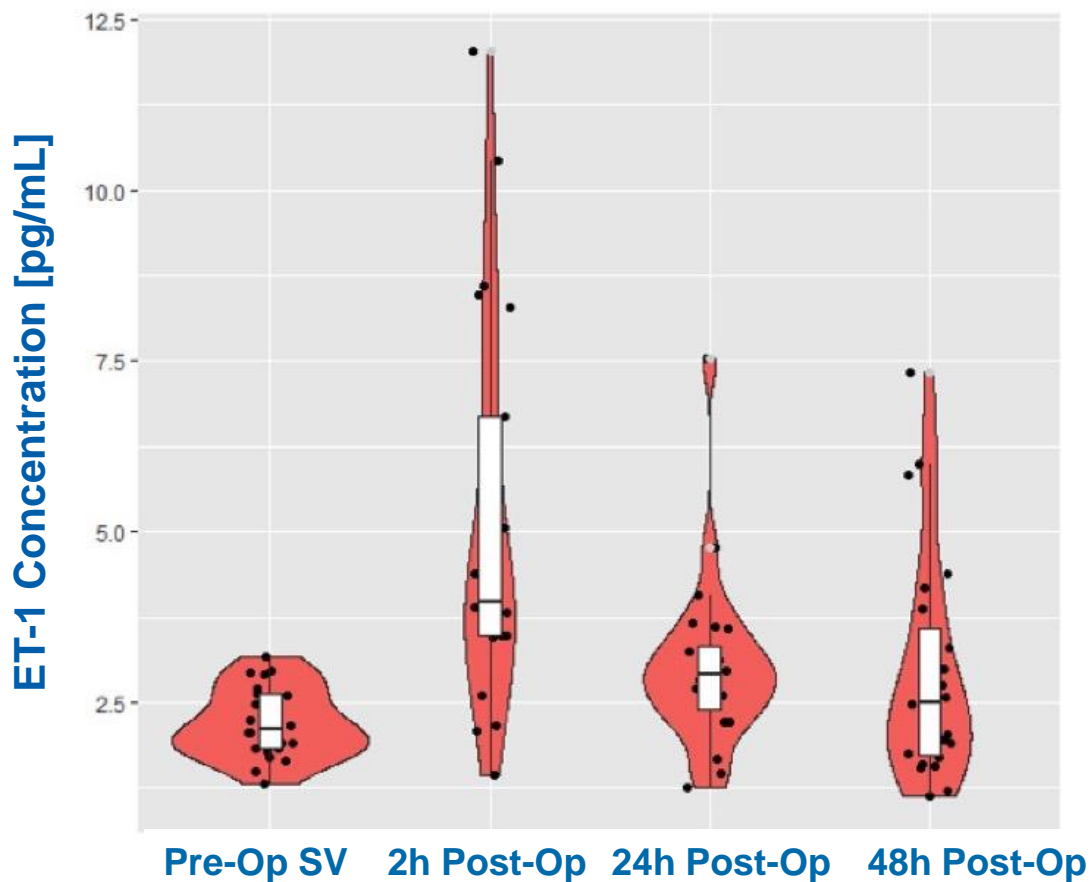
	SVHD Cases (n=26)	Controls (n=39)	P Value
Sex (F)	12 (46%)	11 (28%)	0.13
Weight [kg]	5.5 (5.2-6.2)	7.7 (7.2-8.7)	<0.01
Age [m]	4.5 (3.7-5.7)	6.7 (5.9-8.6)	<0.01
Diagnosis:			
HLHS	13 (50%)		
AVSD	4 (15%)		
DORV	5 (19%)		
DILV	2 (8%)		
TA	2 (8%)		
Stage 1:			
Norwood	14 (54%)		
PA Band	4 (15%)		
Shunt	5 (19%)		
None	3 (12%)		
Mean PA Pressure [mmHg]	12 (11-15)		
PVR[units*m²]	1.7 (1.3-2.3)		
Qp/Qs	1.3 (0.8-1.6)		
O2 Saturation [%]	75 (73-80)		

*Data expressed as median (IQR) or n (%)

Baseline ET-1 Concentration



ET-1 Concentration Rises Following SCPA



Median(IQR):

2.2 (1.8-2.6) 3.9 (3.5-6.7) 2.9 (2.4-3.3) 2.5 (1.7-3.6)

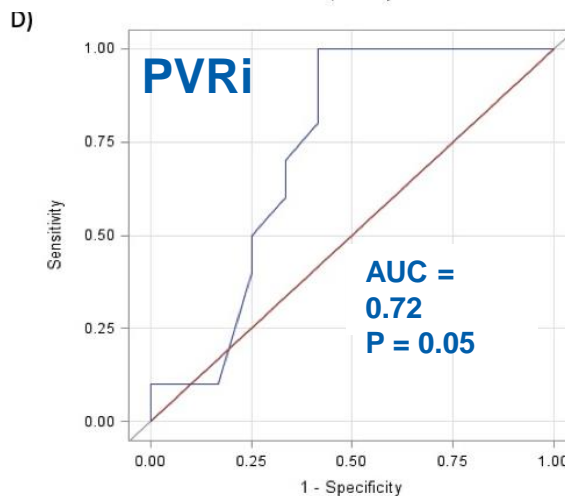
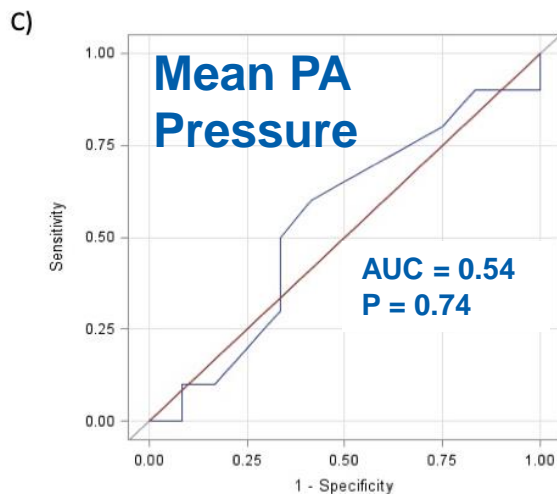
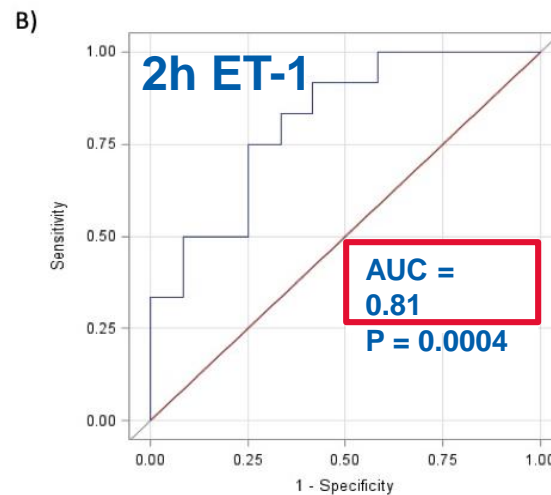
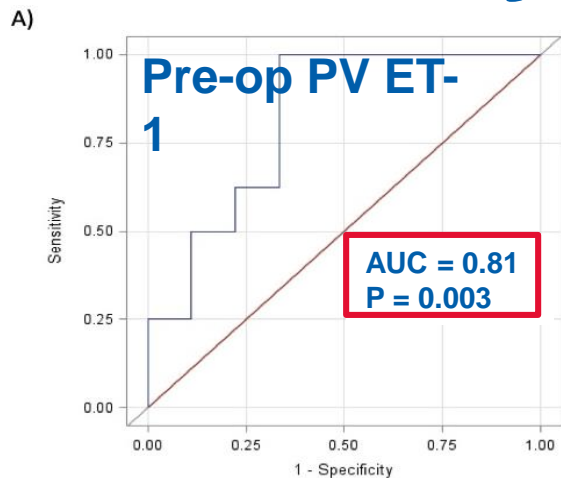
Association Between ET-1 and Hypoxemia

	All SVHD	SVHD subjects ET-1 ≤ 2 pg/mL	SVHD subjects ET-1 >2 pg/mL	P Value
Hypoxemia burden in first 24h post-op (%)	5.1 (1.9-11.2)	4.4 (2.3-8.0)	31.1 (3.3-33.2)	0.07
Hypoxemia burden in first 48h post-op (%)	5.0 (3.0-21.9)	3.8 (2.5-6.5)	24.2 (12.3-37.7)	0.04
Hypoxemia burden in first 72h post-op (%)	5.1 (2.5-17.9)	3.1 (2.0-5.0)	18 (10.0-38.4)	0.04

SVHD population divided by pre-op pulmonary vein ET-1 concentration. P value reflects comparison between high and low ET-1 groups. Data represented as median (IQR).



Association Between ET-1 and 48h Hypoxemia



Summary

- The burden of hypoxemia in the post-op SCPA population is high.
- ET-1 concentration increases significantly immediately after SCPA and then downtrends over the next 48 hrs post-op.
- Subjects with higher pre-op pulmonary vein and 2h post-op systemic vein ET-1 concentration had greater post-op hypoxemia burden.
- Pulmonary vascular resistance and mean pulmonary artery pressure at pre-SCPA catheterization were not significantly associated with post-op hypoxemia.

Speculations

- Chronic pulmonary ET-1 exposure may lead to post-op hypoxemia through impaired pre-SCPA pulmonary vascular growth and/or chronically elevated vascular tone.
- Subjects with more severe acute ET-1 activation during SCPA may experience vasoconstriction that impairs post-op pulmonary blood flow.
- ET-1 shows significant promise as a pre- and post-op biomarker of pulmonary vascular adequacy and potential therapeutic target in the SCPA population.

Acknowledgements

- Primary Mentors:
 - Dr. Davidson
 - Dr. Ivy
 - Dr. Klawitter
- Research team:
 - Ms. Lewis
 - Ms. Khailova
 - Ms. Silveira
- Collaborators:
 - Dr. Mitchell
 - Dr. Morgan
 - Dr. Twite
 - Dr. Di Maria