



**C.S. MOTT
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MICHIGAN MEDICINE

CONGENITAL HEART CENTER

Analysis of inflammatory cytokines in postoperative Fontan pleural drainage

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Please turn off the environment before starting the PowerPoint

Disclosures

There are no disclosures

Strecher Award for Fellow Research

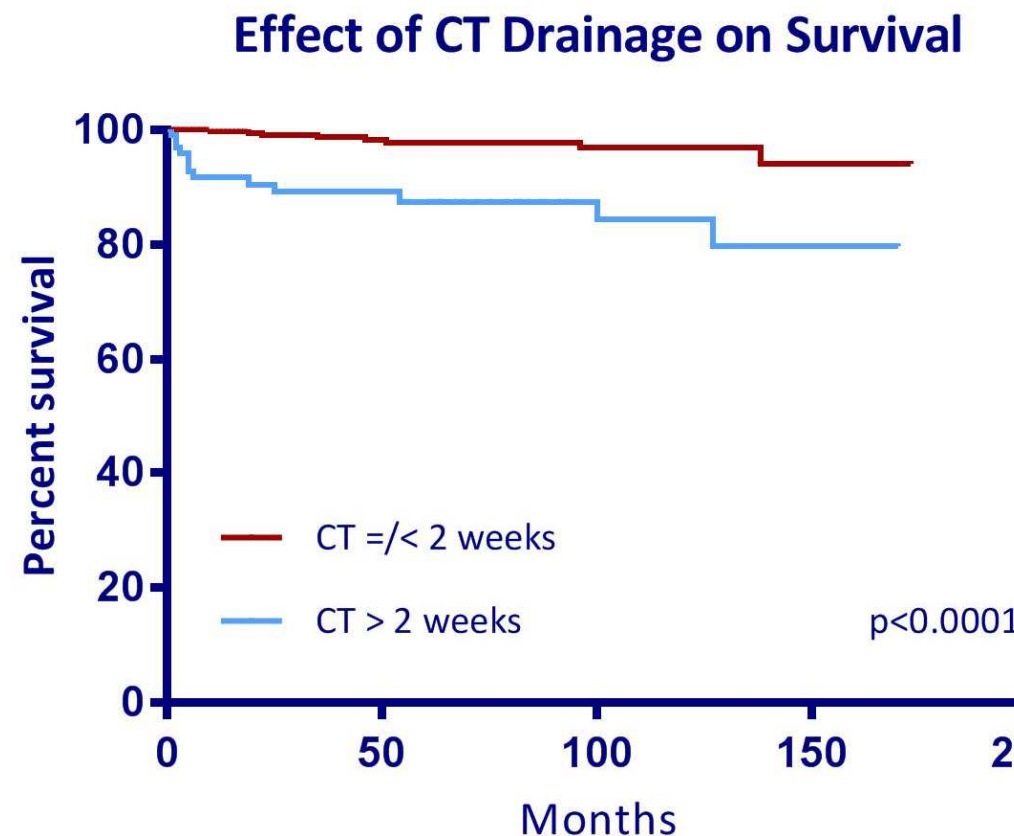
¹Hirsch et al; Annals of Surgery

Background: Prolonged Pleural Drainage

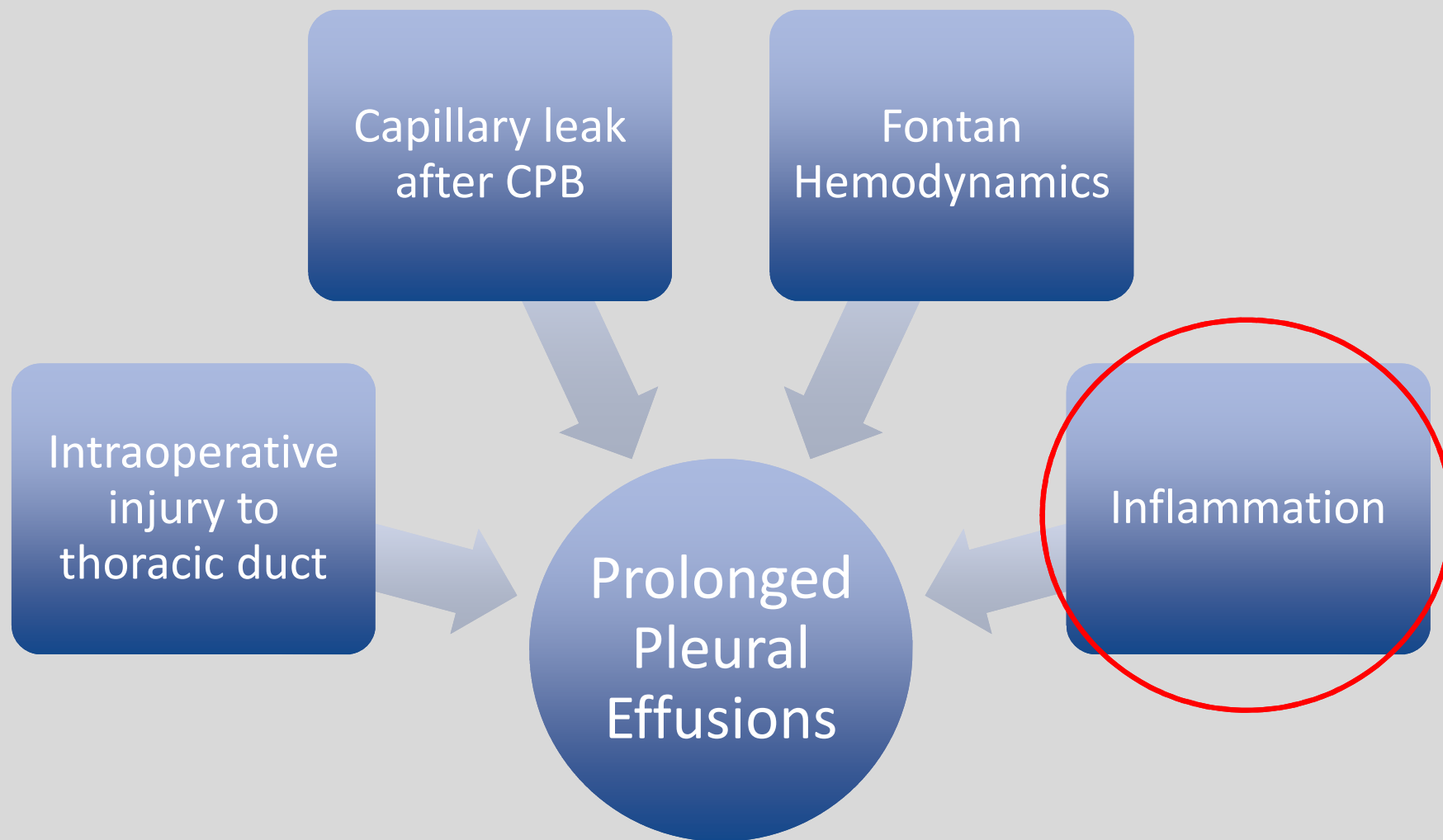
19% with >2 weeks drainage

Principal cause of prolonged hospitalization

Diminished short and long-term survival



Background: Etiologies



Hypothesis

Pleural inflammation is associated with prolonged pleural drainage in postoperative Fontan patients.

Methods

Prospective age-matched cohort study

- 25 Fontan patients
- 15 biventricular patients undergoing cardiopulmonary bypass
- Samples collected until chest tube removal or until second thoracic intervention
- IRB approved

Compared pre-, peri-, postoperative clinical and laboratory data

- Over time (POD 1 to DMD)
- Between groups

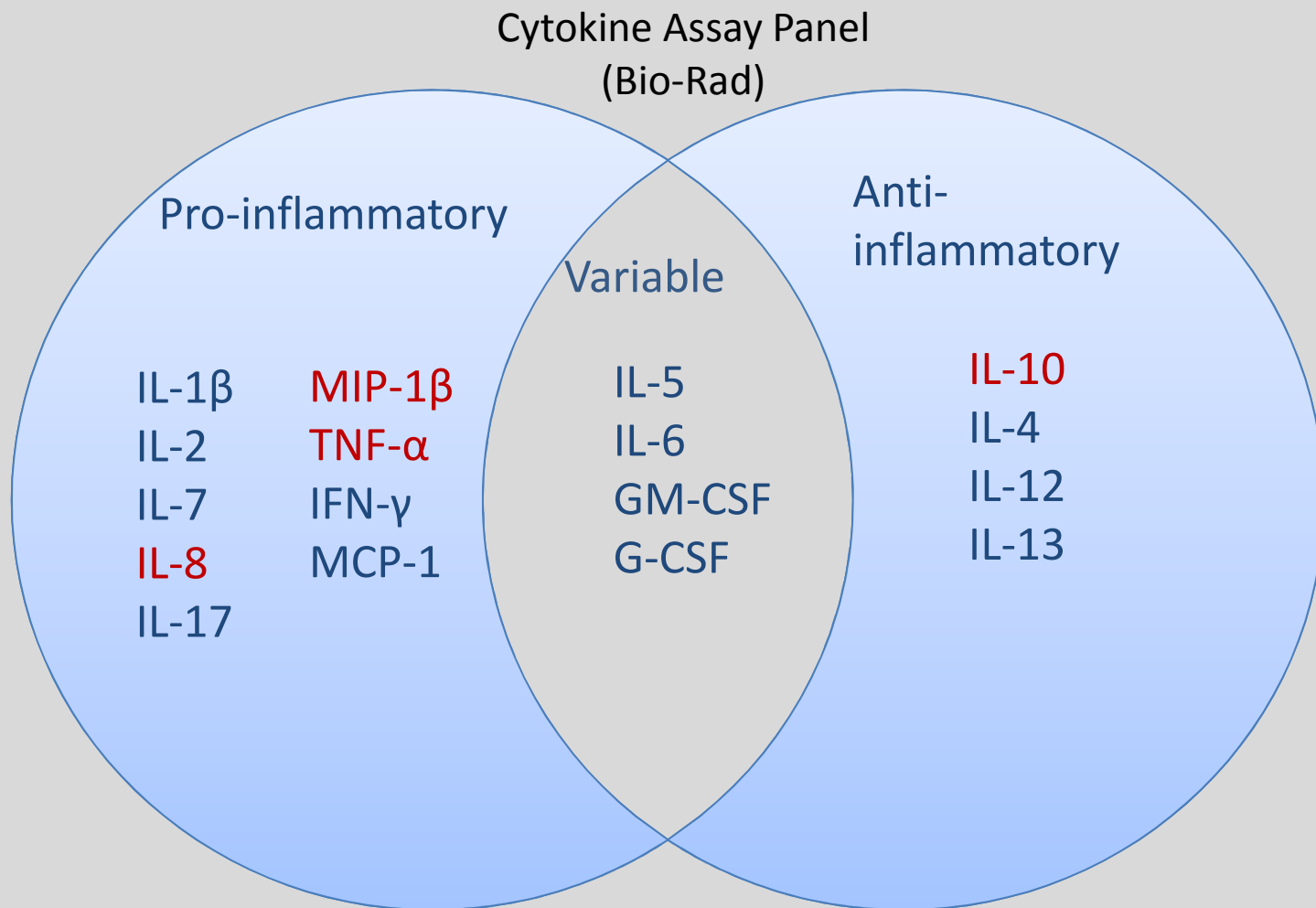
Pleural fluid:
POD 1-4, 7, 10



Blood:
Prior to bypass, P



Methods



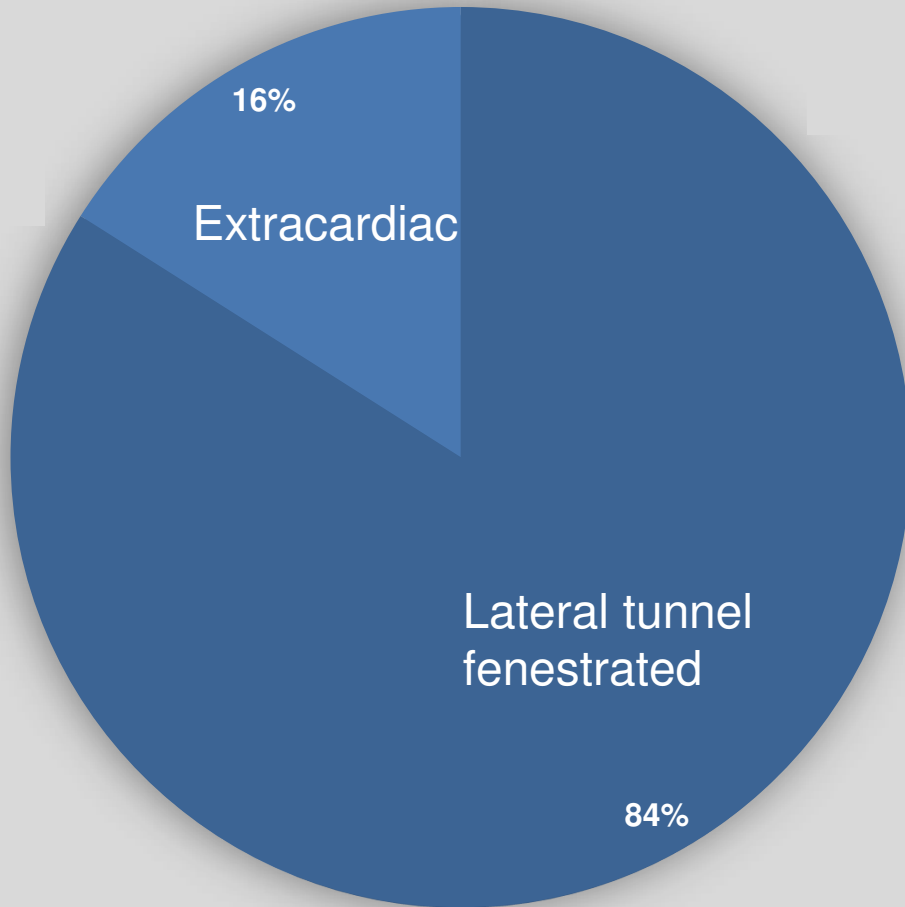
Results

Demographics

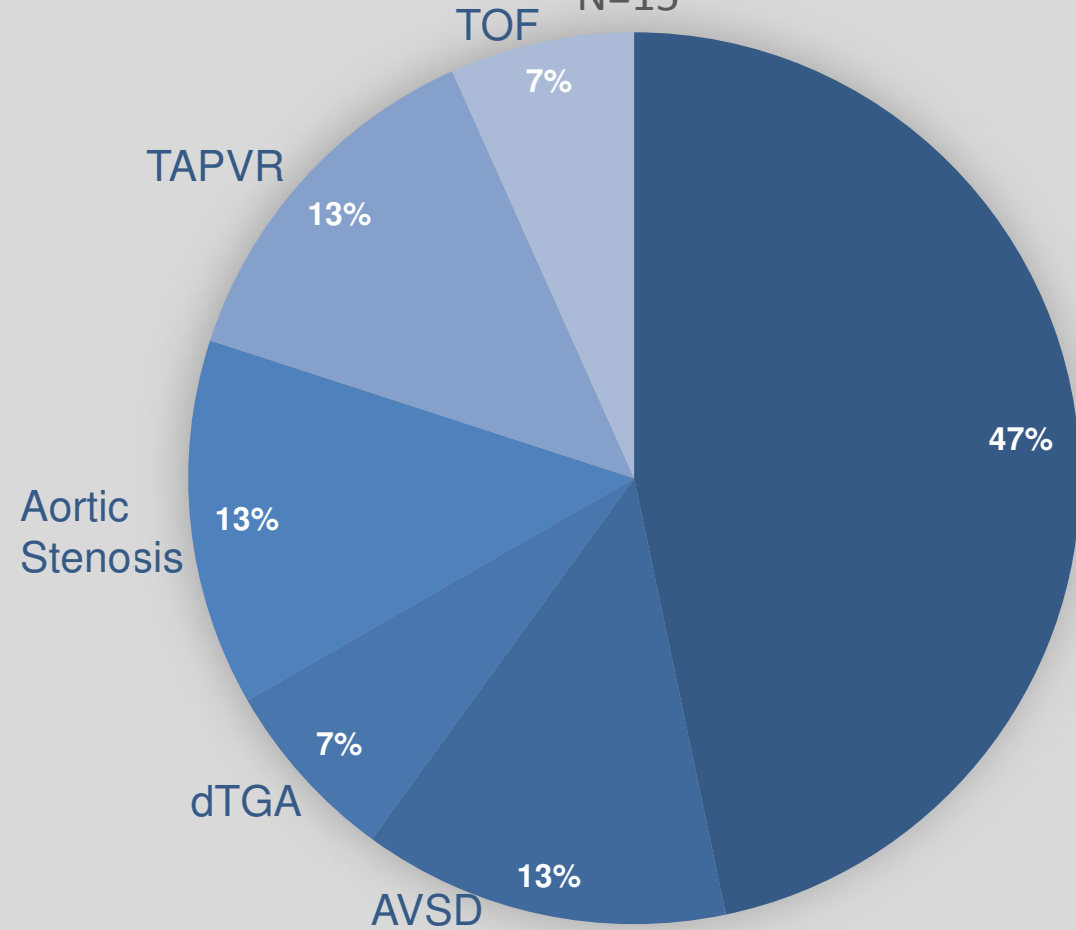
	Fontan (N=25)	Control (N=15)	P-value
Gender			
Male	18 (72%)	7 (47%)	0.11
Race			
Caucasian	22 (88%)	11 (73%)	0.39
Chromosomal Abnormality	1 (4%)	3 (20%)	0.14
Other organ abnormality	15 (60%)	8 (53%)	0.68
Age at surgery (years)	2.5 (2.1-2.9)	3.7 (2.8-3.9)	0.02
Length of stay (days)	11 (9-13)	4 (4-5)	<0.0001

Results

Fontan
N=25



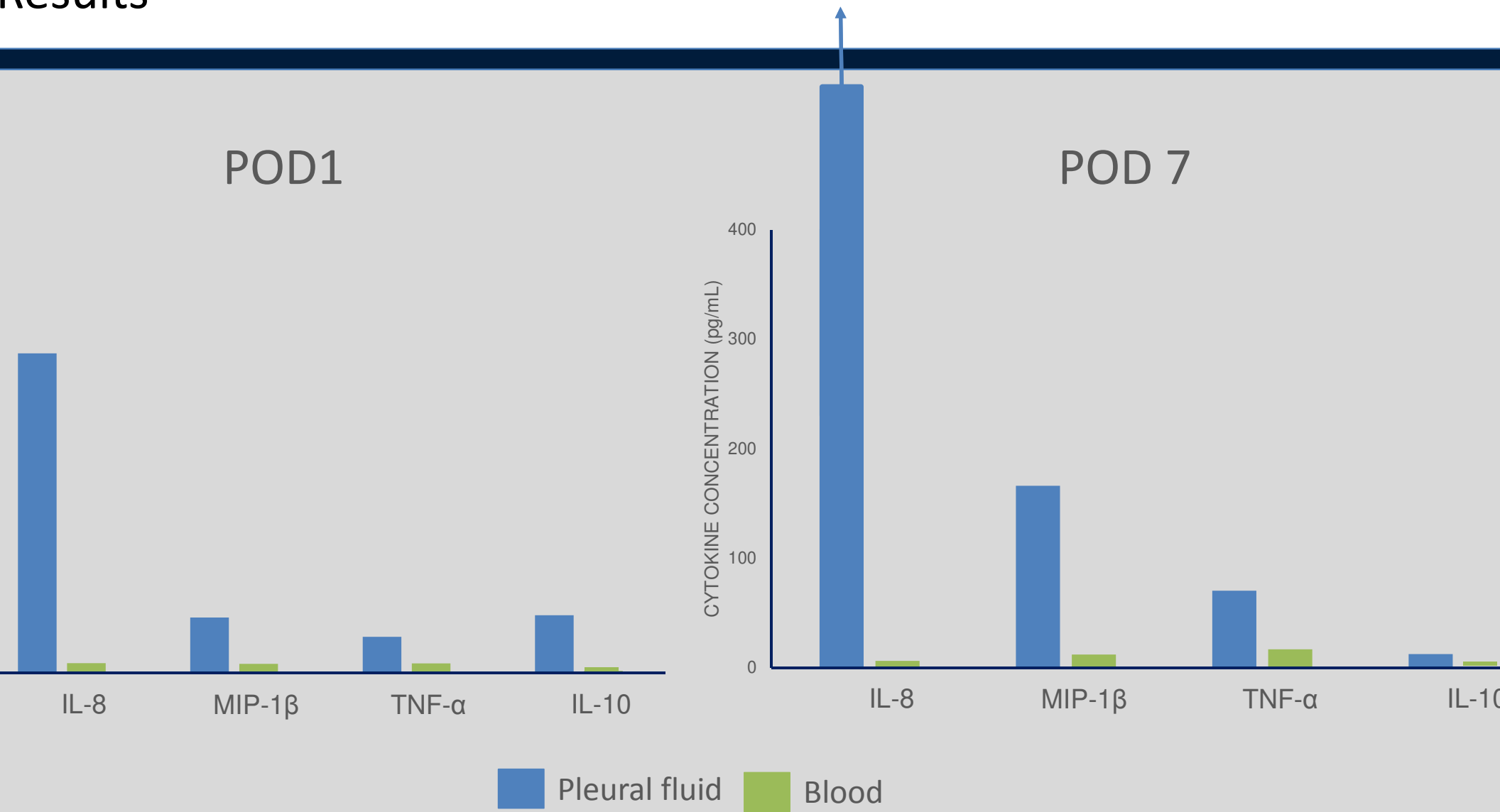
Control
N=15



Results

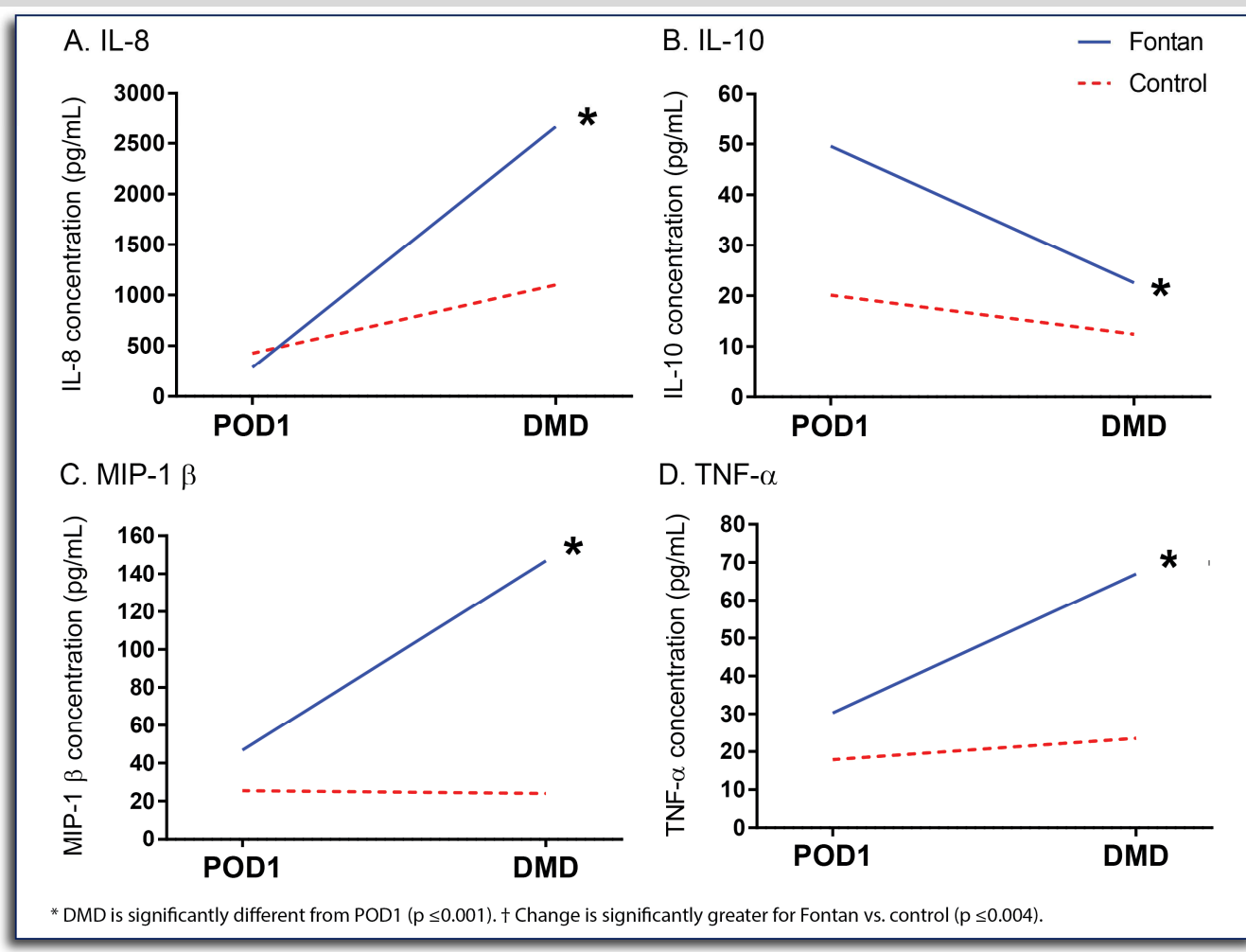
Pleural Drainage	Fontan (N=25)	Control (N=15)	P-value
CT duration, days	11 (9-13)	4 (4-4)	< 0.0001
CT output, mL/day	11.3 (8.7-14.4)	4.8 (3.7-7.8)	0.0001

Results



Results

Change in pleural cytokine concentration from POD1 to DMD



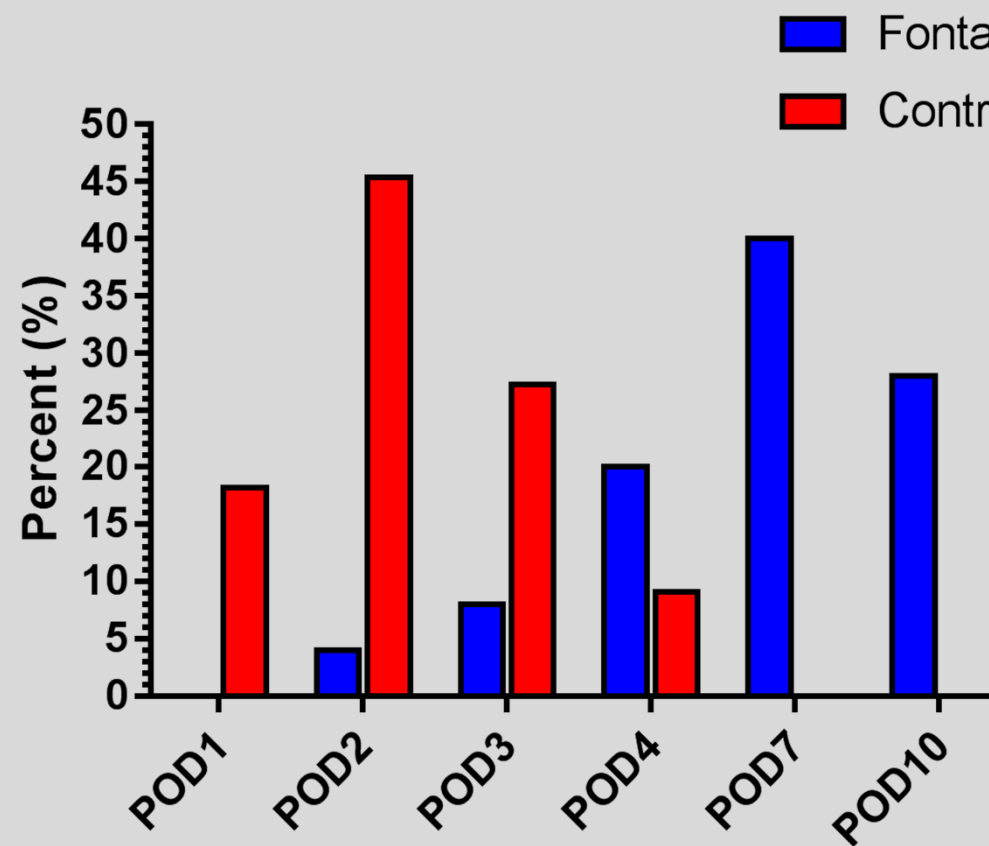
Conclusions

- After cardiac surgery there is inflammation within the pleural space out of proportion to systemic inflammation
- Pro-inflammatory cytokine concentrations are higher and significantly increase with time in postoperative Fontan patients but not in biventricular control patients
 - This suggests an exaggerated ongoing inflammatory response or process that is not a result of cardiopulmonary bypass alone

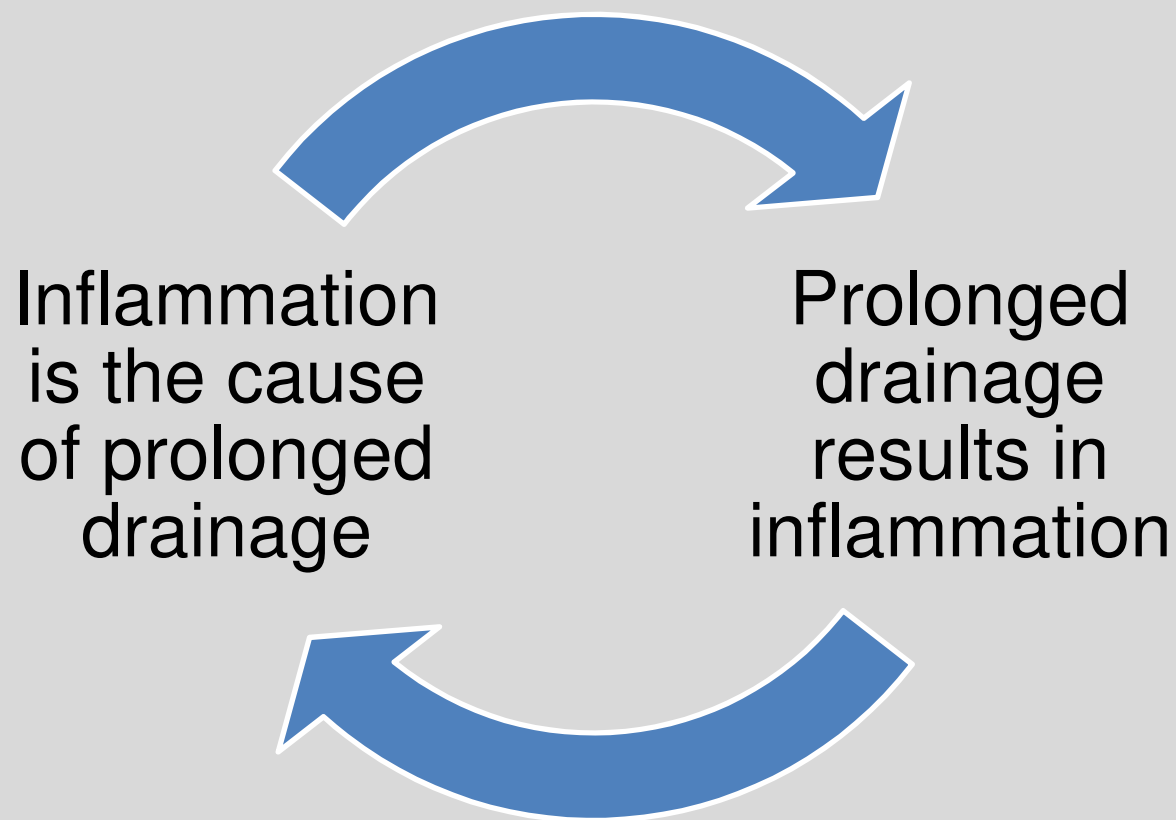
Limitations

- Single center, small sample size
- Controls did not drain past 4 days
- There were no patients who had samples collected more than 10 days postoperatively

Distribution of Day Most Distal (DMD)



Future Directions



Additional studies are needed to determine the mechanism

Acknowledgements

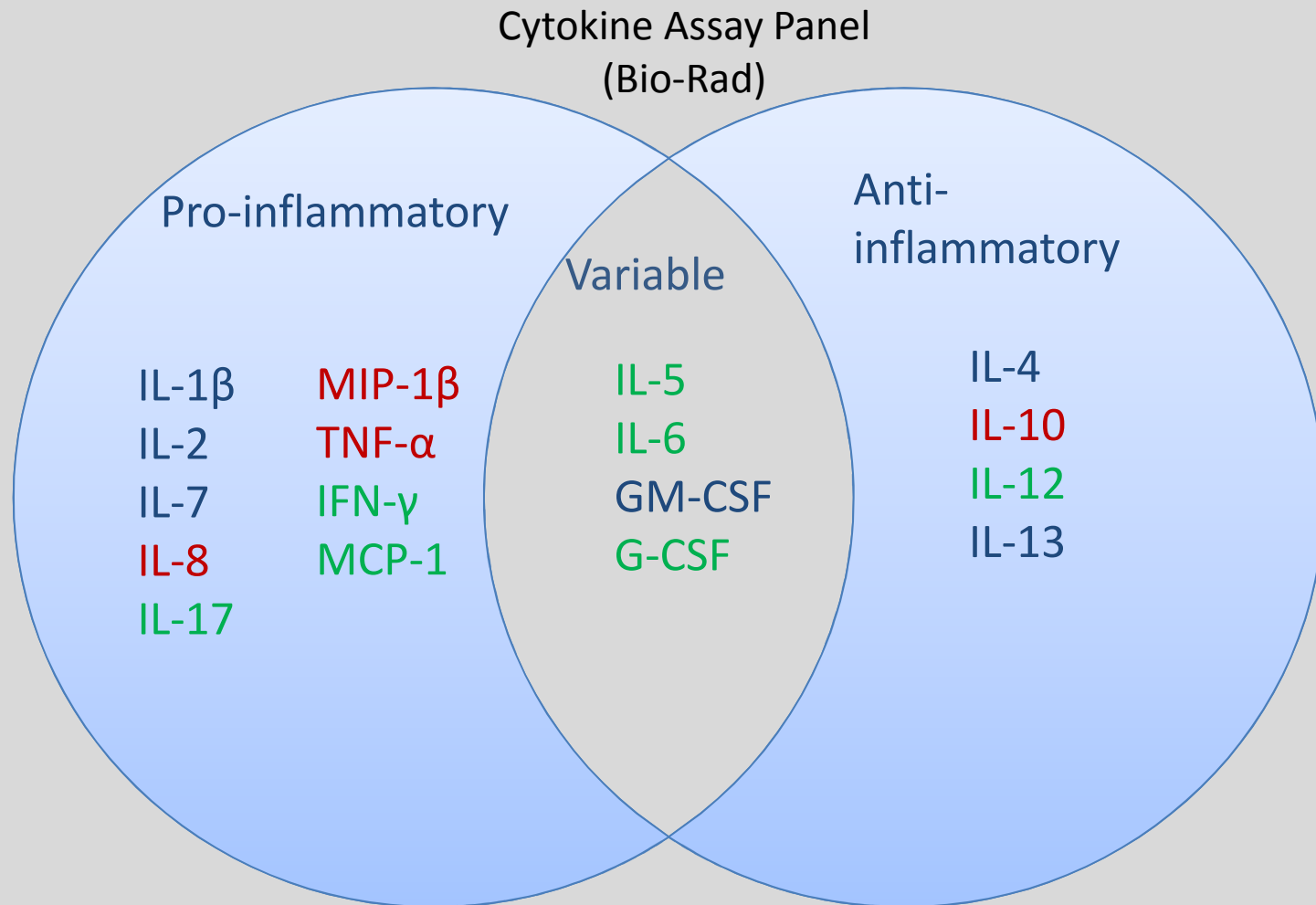


- Clinical Care Coordinators
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 - Katie Jarvis RN BSN
 - Holli Clewis RN BSN
- Laboratory assistance
 - Walker McHugh
 - Kevin Walker

Questions?



Methods



Raw Cytokine Data

	Fontan			Control			Fontan vs Control	
	(n=25)			(n=11)			POD 1	DMD
Cytokine	POD1	DMD	P-value	POD1	DMD	P-value*	P-value	P-value
IL-1 β	1.0 (0.6-5.1)	2.1 (0.6-6.5)	0.60	1.2 (0.6-4.2)	1.6 (0.3-6.8)	0.36	0.73	0.74
IL-2	2.2 (1.1-4.4)	1.8 (1.3-4.6)	0.75	1.1 (0.8-3.0)	1.4 (0.6-1.8)	0.84	0.07	0.22
IL-4	0.2 (0.1-0.3)	0.2 (0.1-0.4)	0.95	0.08 (0.06-0.2)	0.1 (0.05-0.2)	0.50	0.10	0.08
IL-5	33.1 (22.1-47.2)	26.7 (12.4-40.0)	0.34	19.3 (17.2-29.5)	12.5 (9.4-25.5)	0.16	0.03	0.13
IL-6	719.1 (326.3-1107.6)	255.3 (158.4-385.8)	0.0005	987.3 (486.8-1072.1)	305.5 (268.6-606.0)	0.10	0.78	0.51
IL-7	2.4 (1.6-3.7)	0.6 (0.2-2.5)	0.11	1.2 (0.8-1.8)	0.8 (0.6-1.2)	0.21	0.052	0.32
IL-8	283.5 (168.9-1324.9)	2664.4 (920.6-6062.1)	<0.0001	410.8 (103.9-549.8)	1020.6 (266.7-2160.4)	0.07	1.0	0.09
IL-10	49.6 (20.6-88.4)	22.6 (10.1-35.7)	0.001	20.1 (6.7-69.2)	12.4 (7.9-23.2)	0.30	0.06	0.35
IL-12	1.2 (0.5-2.1)	1.4 (0.8-1.8)	0.98	0.6 (0.1-1.1)	0.6 (0.2-1.2)	0.98	0.04	0.08
IL-13	1.0 (0.2-1.7)	1.1 (0.2-2.9)	0.89	0.4 (0.1-0.6)	0.2 (0.1-0.9)	1.0	0.046	0.07
IL-17A	3.3 (2.5-4.6)	5.2 (2.3-7.6)	0.09	1.8 (1.2-2.6)	1.5 (1.1-3.2)	0.46	0.01	0.007
Hu G-CSF	146.0 (44.0-276.0)	25.7 (9.4-56.5)	0.001	69.0 (7.1-223.4)	48.7 (9.4-248.7)	0.16	0.43	0.51
Hu GM-CSF	1.5 (0.2-2.5)	1.5 (0.3-2.9)	0.33	0.4 (0.2-0.7)	0.5 (0.3-0.7)	0.65	0.11	0.08
IFN- γ	15.1 (8.4-20.2)	14.5 (6.6-21.2)	0.91	6.0 (3.3-8.0)	7.4 (4.1-8.6)	0.36	0.004	0.02
MCP-1	836.0 (654.6-974.1)	678.4 (585.7-940.9)	0.08	674.4 (246.3-764.4)	611.2 (478.7-773.0)	0.65	0.015	0.27
MIP-1 β	46.8 (21.0-77.8)	146.9 (79.8-263.1)	<0.0001	25.5 (19.8-40.9)	24.0 (12.0-60.0)	0.65	0.15	<0.0001
TNF- α	30.3 (21.0-39.6)	67.0 (33.8-155.5)	<0.0001	17.9 (12.9-26.5)	23.5 (15.4-31.3)	0.91	0.07	0.0003

Cytokine Functions

- IL-8: chemoattractant for immune cells and has been shown to have increased levels during inflammatory diseases
- MIP-1 β : chemokine produced by macrophages and involved in immune response. It induces the synthesis and release of other pro-inflammatory cytokines
- TNF- α : Inflammatory cytokine produced by macrophages and monocytes during acute inflammation
- IL-10: anti-inflammatory cytokine which inhibits expression of multiple pro-inflammatory cytokines and chemokines.
- IL-17A: involved in induction of pro-inflammatory cytokines, chemokines, and metalloproteases as well as recruitment of neutrophils
- IFN- γ : promotes cytotoxic activity and activates macrophages to kill microbes

Clinical Factors

	Fontan (n=25)	Control (n=15)	P-value
operative characteristics			
Myocardial performance index	0.42 ± 0.11	0.30 ± 0.13	0.00
Tricuspid regurgitation	22	15	
None/Trivial/Mild	3	0	
Moderate or greater			
Right ventricular EDP; mmHg	8 (5-8) n=3	7 (6-15) n=3	
LVEDP	6 (5-8) n=21	9 (6-10) n=3	
RVEDP	11 (10-12) n=24	Range 2-7 n=2	
Right ventricular pressure; mmHg			
operative characteristics			
CPB time, minutes	57 (53-73)	61 (43-110)	0.92
Cross-clamp time, minutes	25 (19-29)	26 (16-56)	0.17
Steroid use	1 (4.0)	1 (6.7)	1.0

Clinical Factors

Operationalization/postoperative characteristics	Fontan N=25	Control N=15	P-value
Hospital length of stay, days	11 (9-13)	4 (4-5)	<0.001
Endotracheal tube duration, days	11 (9-13)	4 (4-4)	<0.001
Endotracheal tube output, mL/kg/day	11.3 (8.7-14.4)	4.8 (3.7-7.8)	0.001
Requirement for pleural drainage			
Low-fat diet	1 (4.0)	0 (0.0)	1.0
NPO and octreotide	1 (4.0)	0 (0.0)	1.0
Thoracic duct ligation/Pleurodesis	0 (0.0)	0 (0.0)	
Planned surgical procedure or catheterization	4 (16.0)	1 (6.7)	0.63
Re-admission for intervention/re-accumulation of pleural fluid	2 (8.0)	1 (6.7)	1.0
Mechanical ventilation required	4 (16.0)	1 (6.7)	0.63
Diaphragm plication	3 (12.0)	0 (0.0)	0.28
Death in 1 st 24 hours	16 (64.0)	6 (40.0)	0.14

Comparing Fontans to Controls

Pleural cytokine concentration on POD1 and DMD, Fontan vs Control

