The Fontan Circulation Shows Decreased Cell Survival And Oxidative Damage

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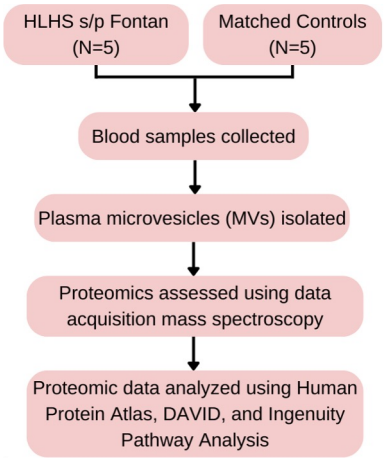
Introduction

Single ventricle congenital heart disease such as hypoplastic left heart syndrome (HLHS) with a Fontan circulation accounts for the largest group of children hospitalized with circulation failure. Advances in the management of single ventricle congenital heart disease has doubled the number of single ventricle survivors. However, greater than 50% of survivors develop heart failure, and standard imaging such as echocardiography and cardiac MRI only detect late changes once dysfunction has set in. The mechanisms of heart failure are also poorly understood, and standard heart failure therapies (b-blockers, ACE inhibitors) lack efficacy.

Our *objective* was to determine a non-invasive, blood-based signature of single ventricle circulation failure. We *hypothesized* that patients with HLHS will have a unique circulating signature reflecting adverse myocardial remodeling which can be leveraged to evaluate the mechanisms of circulation failure, for biological monitoring to predict onset of future circulation failure, risk stratify, and guide therapy.

Materials and Methods



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Results

(A)

	Controls (N=5)	HLHS s/p Fontan (N=5)
Age (years)	14.82±2.2	17.04±2
Sex (Male)	20%	20%
Oxygen Saturation (%)	100	96.91+0.97
NYHA Class	N/A	II/III to IV
Fontan Associated Liver Disease	N/A	80%
Rhythm	Sinus	Sinus
ECHOCARDIOGRAPHY		
Right Ventricular Function	Normal	Moderately to severely decreased
RV Dilation	None	Moderate to severe
Tricuspid Valve Regurgitation	None	Mild
Neo Aortic Regurgitation	None	Trivial

(B)

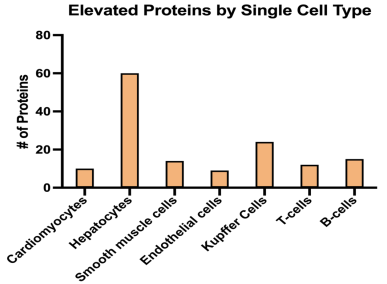

Figure 1: Demographics of HLHS patients vs. controls (A); Number of proteins elevated in single cell type, Circulating MVs were released from cardiomyocytes (troponin, Myosin), endothelial cells (CD31, endothelin), and hepatocytes (alpha1 antitrypsin) based on their cell surface markers (B).

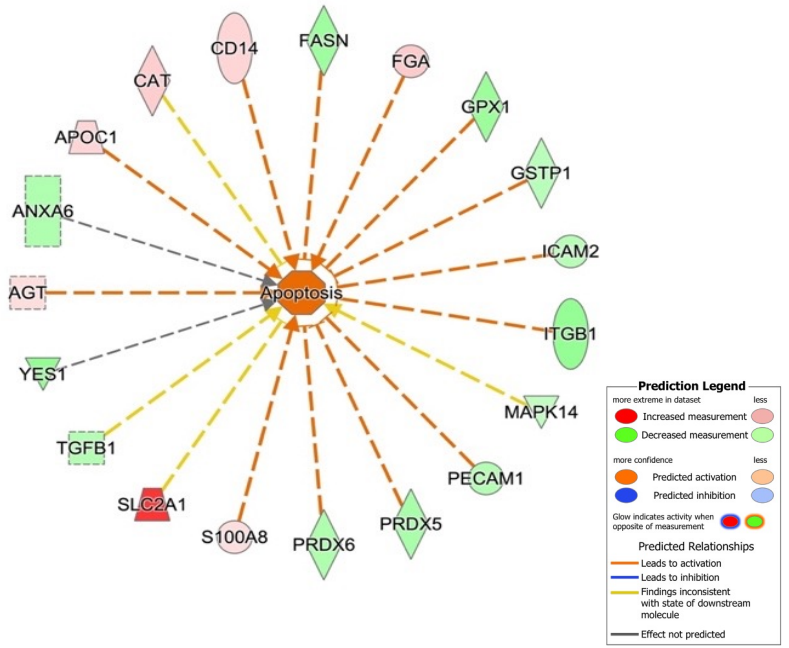

Figure 2: Plasma proteomics show an upregulation in; cell survival and viability pathways are downregulated. Upregulated proteins (N=27) implicated cell death pathways (Solute carrier family 2, Angiotensinogen, facilitated glucose transporter member, Annexin 5/6); while downregulated proteins (N=88) implicated impaired cell survival (Tyrosine-protein kinase Yes, endothelial growth factors).

Discussion and Conclusions

Past studies have looked at heart failure biomarkers in other patient populations or for signs of early death, however this is the first study to evaluate the circulating signature of single ventricle patients. Our objective was to identify a noninvasive signature of organ remodeling. We found that circulating MVs from patients with HLHS s/p Fontan were released from the heart, blood vessels, and liver. The MV protein cargo implicates heightened cell death, oxidative damage and impaired cell survival (Figure 2), thereby providing insight into the mechanisms of Fontan associated circulation failure.

This study is limited by its small sample size. It is also unclear whether the circulating proteins are reflective of cardiac remodeling. Future studies will evaluate cardiac muscle along with plasma proteomics to address this limitation.

Acknowledgments

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