ALTERATIONS OF THE KYNURENINE/TRYPTOPHAN PATHWAY IN SINGLE VENTRICLE INFANTS UNDERGOING STAGE 3 PALLIATION

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Background

Single ventricle heart disease (SVHD) is a severe form of congenital heart defect (CHD) which is characterized by a single functional ventricle. The incidence of SVHD is approximately 2-8 per 10,000 live births. Infants undergoing staged palliation for single ventricle heart defects represent a uniquely vulnerable patient population. There are currently no validated biomarkers to guide risk evaluation and clinical decision making prior to Stage 3 palliation (S3P). Analysis of the Kynurenine/Tryptophan pathway (KP) after Stage 2 Palliation has shown disturbances in the KP in patients with SVHD compared to controls. This investigation aims to analyze the KP for patients undergoing Stage 3 Palliation.

Objectives

Compare concentrations of KP metabolites in infants undergoing staged palliation compared to controls.
Compare concentrations of KP metabolites in patients undergoing staged palliation over the 48h following surgery.

Methods

- **Subjects**

74 infants undergoing S3P at the Children's Hospital of Colorado were enrolled during pre-operative evaluation with blood samples collected at pre-operation, 2h, 24h, and 48h post-operation. A blood sample was also obtained from 47 age-matched healthy controls undergoing non-cardiac surgery requiring IV access.

- **Clinical Data**

Clinical data were collected from the electronic medical record. Metabolite concentrations were quantified using tandem mass spectroscopy.

- **Kynurenine Pathway Analysis**

Case control analysis : KP Metabolite concentrations for cases (patients undergoing staged palliation for SVHD) and controls were compared using student's *t*-tests.
Time series analysis: KP Metabolite concentrations pre op were compared to 2, 24, and 48h post op using repeated measures ANOVA. Post-hoc comparisons of metabolite concentrations over time were carried out using student's *t*-tests.

Results

Table 1: Demographics

	Overall	Case	Control	p
n	127	80	47	
sex = 2 (%)	74 (58.3)	47 (58.8)	27 (57.4)	1.000
weight (mean (SD))	14.62 (2.69)	13.94 (2.19)	15.77 (3.06)	<0.001
ageondos (mean (SD))	40.43 (10.66)	39.30 (10.70)	42.35 (10.43)	0.120
los (mean (SD))	12.88 (14.71)	12.88 (14.71)	NaN (NA)	NA
cpb (mean (SD))	125.50 (38.65)	125.50 (38.65)	NaN (NA)	NA
xcl (mean (SD))	23.25 (30.50)	23.25 (30.50)	NaN (NA)	NA

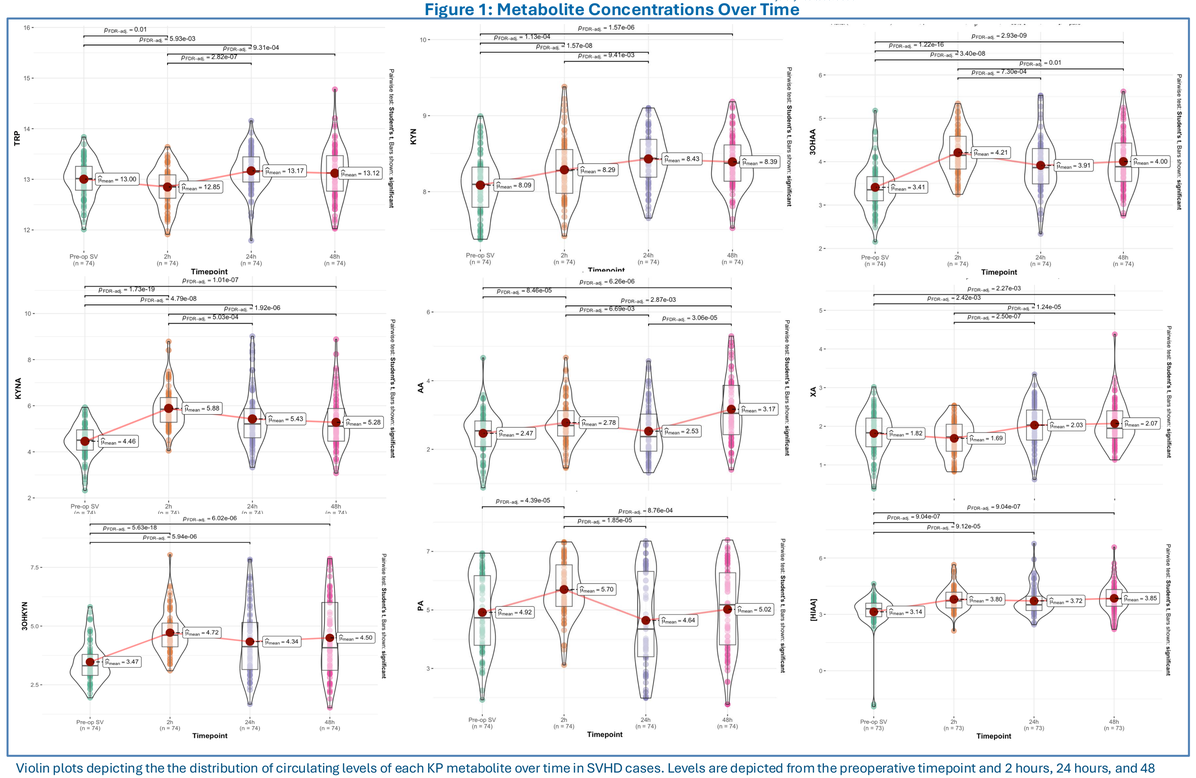
Demographic information for included case and control subjects. Ageondos = age on date of surgery, los = length of stay, cpb = cardiopulmonary bypass time (cases only), xcl = cross clamp time (cases only).

Table 2: Adjusted Case Control Comparison

Metabolite	contrast	estimate	FC	FC_lower95	FC_upper95	percent_change	p.value	p.adj
3OHAA	**Case - Control**	**-0.321**	**0.800**	**0.709**	**0.904**	**-19.966**	**0.000**	**0.000**
3OHKYN	**Case - Control**	**0.582**	**1.497**	**1.210**	**1.853**	**49.727**	**0.000**	**0.000**
AA	Case - Control	-0.061	0.959	0.794	1.158	-4.126	0.659	0.725
KYN	**Case - Control**	**-0.419**	**0.748**	**0.685**	**0.818**	**-25.181**	**0.000**	**0.000**
KYNA	Case - Control	-0.014	0.990	0.831	1.180	-0.977	0.912	0.912
PA	**Case - Control**	**-0.949**	**0.518**	**0.383**	**0.700**	**-48.201**	**0.000**	**0.000**
QA	Case - Control	0.227	1.171	0.956	1.433	17.064	0.125	0.196
SER	**Case - Control**	**-0.609**	**0.656**	**0.517**	**0.831**	**-34.449**	**0.001**	**0.002**
TRP	**Case - Control**	**-0.348**	**0.786**	**0.719**	**0.859**	**-21.415**	**0.000**	**0.000**
XA	Case - Control	-0.058	0.961	0.850	1.086	-3.944	0.517	0.632
[HIAA]	Case - Control	0.120	1.087	0.890	1.328	8.700	0.411	0.565

Baseline KP metabolite values in cases vs controls compared using student's *t*-tests. Statistical significance is indicated by bolded text. 3OHAA = 3-hydroxyanthranilic acid, 3OHKYN = 3-Hydroxykynurenine, AA = anthranilic acid, KYN = Kynurenine, KYNA = Kynurenic acid, PA = picolinic acid, QA = quinolinic acid, SER = serotonin, TRP = tryptophan, XA = xanthurenic acid, [HIAA] = 5-hydroxyindoleacetic acid

Figure 1: Metabolite Concentrations Over Time



Violin plots depicting the the distribution of circulating levels of each KP metabolite over time in SVHD cases. Levels are depicted from the preoperative timepoint and 2 hours, 24 hours, and 48 hours post operatively. Mean concentration is shown with red circles connected by red lines, while outliers are depicted above and below the means. Timepoints are indicated by colors: green is preoperatively, orange is 2 hours, blue is 24 hours, and pink is 48 hours post operatively.

Conclusions

- Statistically significant differences in metabolite concentration are observed between cases and controls in for all KP metabolites except for AA, KYNA, QA, XA, and HIAA
- Children undergoing S3P experience a disturbance in tryptophan metabolism at baseline compared to healthy controls, with most metabolites decreased from control levels (3OHAA, KYN, PA, SER, TRP)
- Over time from pre-op to post-op, KP metabolites tend to rise, with some peaking at 2h post op (3OHAA, 3OHKYN, KYNA, PA, SER), and others continuing to increase until the 48h mark (AA, [HIAA]).

Implications

- These preliminary results suggest that there are differences in KP metabolite concentrations between cases and controls and in cases over time.
- Future analysis will incorporate patient outcomes including length of stay, duration of intubation, and post operative oxygen requirement in order to determine the clinical significance of these differences in tryptophan metabolism for patients undergoing staged palliation for SVHD.

Disclosures

No conflicts of interest to disclose