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# Norepinephrine levels in children with single ventricle circulation☆

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ABSTRACT

Elevated plasma norepinephrine levels are a strong independent predictor of mortality in adults with heart failure with systolic dysfunction, and provide the mechanistic basis to its therapeutic paradigm. The pathogenesis of heart failure in the single ventricle circulation is unknown. It remains controversial whether conventional neurohormonal blockade in this population is beneficial. We hypothesize that norepinephrine levels can be elevated in children with single ventricle circulation and that it is associated with a poor outcome.

Norepinephrine levels were collected from 22 consecutive single ventricle and 7 control patients at the time of catheterization. The disease group was followed for the development of heart failure and a composite outcome of death or transplant.

Median age at norepinephrine level was 2.4 years (interquartile range 93 days–16.8 years) and follow-up duration was 9.8 years (range 75 days–10.5 years), during which 5 patients (23%) met a composite outcome of either death (n = 4) or transplantation (n = 1). While ventricular dysfunction and individual invasive hemodynamic parameters were not predictive of subsequent composite outcome, a norepinephrine level > 369 pg/mL at time of catheterization was associated with a decreased freedom from the composite outcome.

In this study of children with single ventricle circulation, elevated norepinephrine levels were observed and were associated with a poor outcome. Consideration should be given to the further study of the role of neurohormonal activation and potentially its blockade, currently used for heart failure from systolic dysfunction, in the management of this high risk congenital heart disease population.

## 1. Introduction

The long-term outcome of patients with single ventricle circulation remains problematic despite good surgical results. Numerous major cardiovascular events can occur over the lifespan of single ventricle patients. These events typically emanate from failure of the cavo-pulmonary side of the circulation where there is no pumping chamber, or from the systemic side of the circulation such as ventricular dysfunction. Given the high-risk nature of the single ventricle circulation, consideration has been given to "protecting" the cardiovascular system with anti-thrombotics, pulmonary vasodilators, afterload reduction, and anti-remodeling medications. However, the only randomized multicenter trial of medical heart failure therapy in single ventricle patients to date did not find significant differences in the primary endpoint of weight-for-age or cardiovascular specific secondary endpoints after 14 months of treatment with enalapril starting in infancy before palliation with Glenn shunt [1]. Despite the large amount of robust mechanistic and clinical trial data supporting the benefits of renin-angiotensin-aldosterone system and beta-adrenergic receptor blockade in adults with systolic heart failure, it remains unclear whether these mechanisms are also involved in mediating heart failure in single ventricle patients. Without such knowledge, further clinical trials of neurohormonal blockade in single ventricle patients will remain unattractive. Plasma norepinephrine plays a pivotal role in the regulation of the renin angiotensin aldosterone system [2,3], is a strong independent predictor of progression of chronic heart failure from systolic dysfunction in adults [4–6], and is the basis for the successful clinical results of beta-adrenergic blockade in this population [2]. Therefore, we undertook an assessment of norepinephrine levels and long term clinical outcomes in children with single ventricle circulation.

## 2. Methods

After Institutional Review Board approval and informed consent obtained from all participants, we prospectively enrolled 22

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consecutive single ventricle patients and 7 healthy control subjects between January 2001 and December 2002 who were scheduled for cardiac catheterization for the collection of plasma norepinephrine. Each had anatomy and physiology such that the cardio-surgical consensus was for palliation under the single ventricle circulation pathway. We also enrolled 7 otherwise healthy children with normal cardiac structure and function who required catheterization for invasive electrophysiological testing to provide comparative normative norepinephrine levels as normative values for this neurohormone in pediatric heart disease or healthy children are not well established. All catheterizations were performed under deep sedation or general anesthesia. Blood samples for plasma norepinephrine levels were collected from a central venous site at least 30 min after commencement of sedation/anesthesia. Samples were collected in cold heparinized tubes and transported on ice and immediately centrifuged. The plasma fraction was stored at − 20 °C until batch measurement of norepinephrine levels by conventional high-pressure liquid chromatography methodology [7]. Invasive hemodynamics at time of catheterization, echocardiogram results closest to catheterization, and all pertinent clinical data, including determining whether the patients had manifestations of heart failure as notated in the medical records were collected through March 2012.

All numerical data are presented as counts with percentages or medians with interquartile range. Group comparisons were made using Fisher's exact, Wilcoxon rank-sum, two-sample binomial, and log rank tests of time to event analyses as appropriate. All analyses were performed using Stata13 (StataCorp, College Station, Texas).

## 3. Results

The clinical characteristics of the study participants are described in Table 1. The median age of the single ventricle patients at time of norepinephrine collection at catheterization was 2.4 years (interquartile range 93 days–16.8 years). The single ventricle group was heterogeneous in terms of their palliative stage: 14 were at the cavopulmonary stage and 8 had an aortopulmonary shunt. Most were receiving cardiovascular medications. As compared to the control group, the single ventricle group was younger and smaller.

**Table 1**
Clinical characteristics in the single ventricle patients and controls.

| | Single ventricle (n = 22) | Controls (n = 7) | p Value |
|---|---|---|---|
| Age (years) | 2.4 (0.5–7.9) | 15.3 (12.1–17.3) | < 0.001 |
| Male sex (%) | 17 (77) | 5 (71) | 0.75 |
| Weight (kg) | 11.1 (6.4–18.7) | 54 (38.1–65.3) | < 0.001 |
| Height (cm) | 81.0 (67.8–109.0) | 168 (145.0–172.0) | < 0.001 |
| Weight %-tile | 7 (1–50) | 58 (8–82) | 0.14 |
| Height %-tile | 20 (4–54) | 24 (5–52) | 0.68 |
| Duration of follow-up (months) | 9.8 (5.9–10.3) | NA | |
| Stage of palliation (%) | | | |
| Aortopulmonary shunt | 8 (36) | | |
| Glenn | 10 (45) | | |
| Fontan/Kawashima | 4 (18) | | |
| Morphological right ventricle (%) | 7 (32) | NA | |
| Cardiovascular medications | Any 15 (68)<br>Diuretics 7 (32)<br>Mineralocorticoid antagonists 1 (5)<br>Angiotensin converting enzyme inhibitor 13 (59)<br>Digitalis 9 (41)<br>Beta blockers 1 (5) | 4 (57)[a] | |

Values are counts with % or medians with interquartile. Aortopulmonary shunt can be surgical or native.
[a] All were on atenolol.

**Table 2**
Hemodynamics and plasma norepinephrine levels in the single ventricle patients and controls.

| | Single ventricle (n = 22) | Controls (n = 7) | p Value |
|---|---|---|---|
| Mean pulmonary artery pressure mm Hg[a] | 12 (10–14) | NA | |
| Mean atrial pressure mm Hg[a] | 7 (5–9) | NA | |
| Mean ventricular end-diastolic pressure mm Hg[a] | 8 (6–10) | NA | |
| Oxygen saturation %[a] | 82 (77–86) | NA | |
| Norepinephrine level pg/mL | 152 (49–359) | 75 (68–284) | 0.65 |
| Aortopulmonary shunt n = 8 | 207 (99–367) | NA | 0.34[b] |
| Cavopulmonary shunt n = 14 | 105 (26–268) | NA | |
| Death or transplant | | NA | 0.09 |
| No (17) | 139 (26–241) | | |
| Yes (5) | 369 (105–1128) | | |
| Heart failure | | | |
| No (16) | 121 (25–244) | NA | 0.12 |
| Yes (6) | 254 (108–792) | | |
| Norepinephrine level cutoff of 369 pg/mL | | | |
| Level < 369 and no HF | 14/17 (82) | | 0.06[c] |
| Level ≥ 369 and HF | 3/5 (60) | | |
| Level < 369 and no death/transplant | 15/17 (88) | | 0.02[c] |
| Level ≥ 369 and death/transplant | 3/5 (60) | | |

Values are counts with % or medians with interquartile range. Aortopulmonary shunt can be surgical or native.
[a] Sample size in single ventricle group = 19.
[b] Comparison between single ventricle subgroups.
[c] Two-sample binomial test.

Median follow-up of the single ventricle group was 9.8 years (75 days–10.5 years) and all but 2 patients went on to have completion of Fontan. Table 2 shows plasma norepinephrine levels in relation to the stage of single ventricle palliation, invasive hemodynamics, and the composite poor outcome of death/need for heart transplant. Median norepinephrine level was 152 pg/mL among single ventricle patients and 75 pg/mL among controls (p = 0.70). Within the single ventricle group, median norepinephrine levels in cavopulmonary patients was 105 pg/mL versus 207 pg/mL in aortopulmonary shunt patients (p = 0.34).

Table 3 describes the important cardiovascular events for each single ventricle patient. Heart failure was present at the time of norepinephrine collection in 3 patients while 3 others developed heart failure at 70 days, 1.6, and 7.3 years later. The 6 patients with heart failure had a median plasma norepinephrine level of 254 pg/mL versus 121 pg/mL for those who did not at the time of catheterization (p = 0.12). During follow-up, 5 of 22 single ventricle patients (1 aortopulmonary shunt, 2 Glenn, and 2 Fontan palliated patients at time of norepinephrine collection) died or received transplantation. These patients showed a trend toward higher norepinephrine levels compared to those who did not die or receive a transplant (369 pg/mL vs. 139 pg/mL; p = 0.09). Using this median norepinephrine level to stratify the single ventricle cohort, 14/17 with norepinephrine level < 369 pg/mL at catheterization did not have heart failure at or after norepinephrine testing (p = 0.06); 15/17 did not die or require transplant listing (p = 0.02, Table 2). When patients were examined in a time to event estimate, stratified using the same norepinephrine cutoff of 369 pg/mL, those below this level had increased freedom from the development of new heart failure symptoms (p = 0.03, Fig. 1a) and from the composite outcome of death/transplantation (p = 0.02, Fig. 1b). In both analyses, the separation of the single ventricle subgroups by this norepinephrine level to the event of interest was evident early. Of note, single ventricle patients with norepinephrine < 369 pg/mL remained free of death/transplant up to > 6 years.

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