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Angiotensin-converting enzyme inhibition and pre-superior cavopulmonary connection haemodynamics in infants with single-ventricle physiology

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Abstract

Introduction: Preliminary animal and human data suggest that angiotensin-converting enzyme inhibition has a role in pulmonary vascular remodelling. We sought to assess the effect of ACEi versus placebo on pulmonary artery pressure and transpulmonary gradient amongst infants undergoing single-ventricle palliation. *Materials and methods:* Using the publicly available Pediatric Heart Network Infant Single-Ventricle trial dataset, we compared mean PA pressure at pre-superior cavopulmonary connection catheterisation (primary outcome), transpulmonary gradient, pulmonary-to-systemic flow ratio, and post-SCPC oxygen saturation (secondary outcomes) in infants receiving enalapril versus placebo. *Results:* A total of 179 infants underwent pre-SCPC catheterisation, of which 85 (47%) received enalapril. There was no difference between the enalapril and placebo group in the primary and the secondary outcomes. Mean PA pressure in the enalapril group was 13.1 ± 2.9 compared to 13.7 ± 3.4 mmHg in the placebo group. The transpulmonary gradient was 6.7 ± 2.5 versus 6.9 ± 3.2 mmHg in the enalapril and placebo groups, respectively. The pulmonary-to-systemic flow ratio was 1.1 ± 0.5 in the enalapril group versus 1.0 ± 0.5 in the placebo group and the post-SCPC saturation was 83.1 ± 5.0% in the enalapril group versus 82.2 ± 5.3% in the placebo group. In the pre-specified subgroup analyses comparing enalapril and placebo according to ventricular morphology and shunt type, there was no difference in the primary and secondary outcomes. *Conclusion:* ACEi did not impact mean pulmonary artery pressure or transpulmonary gradient amongst infants with single-ventricle physiology prior to SCPC palliation.

Patients with single-ventricle CHD who have undergone Fontan palliation experience pathologic pulmonary vascular remodelling with a secondary elevation of the pulmonary vascular resistance.[1] These maladaptive changes may contribute to decreased systemic ventricle preload, low cardiac output, exercise intolerance, and ultimately failure of the Fontan circulation.[2]

Animal studies of hypoxia and shunt-induced pulmonary hypertension have suggested that the renin–angiotensin–aldosterone system may play a role in pulmonary vascular remodelling. In chronically hypoxic rat lungs, administration of an angiotensin 2 receptor antagonist resulted in lower pulmonary artery pressure compared to rats receiving saline.[3] A similar finding has been reported using quinapril in animal models of pulmonary hypertension induced by hypoxia[4] and in animal models of aortopulmonary shunt-induced pulmonary hypertension.[5] In clinical studies, main pulmonary artery tissue extracted during lung or heart–lung transplant in patients with idiopathic pulmonary hypertension showed that the renin–angiotensin pathway is expressed in the smooth muscle of pulmonary arteries and may be involved in human pulmonary vascular remodelling.[6]

Angiotensin-converting enzyme inhibitors have been used in paediatric heart failure associated with left-to-right shunts or chronic valvular regurgitation because they reduce systemic vascular resistance and left-to-right shunt.[7–10] Amongst single-ventricle patients, ACEi have been shown to decrease ventricular filling pressure in older children with Fontan physiology[11,12] while pulmonary hypertension therapies aimed at modulating the pulmonary vascular resistance in this patient population have yielded mixed results.[13–18] Adults with chronic heart failure treated with ACEi have been shown to have lower PA pressure with short term use.[19] However, it is uncertain whether this is due to a primary remodelling effect of ACEi on the pulmonary vascular bed or a secondary decrease in PA pressure due to lower left atrial pressure.

Given the importance of low PA pressure and low pulmonary vascular resistance for long-term Fontan health, we sought to assess the impact of ACEi on the pulmonary vascular bed in infants with SV-CHD using the Pediatric Heart Network Infant Single Ventricle trial dataset. The original ISV trial showed that enalapril in the first year of life was not associated with

improved somatic growth, ventricular function, or heart failure severity,[20] but the ISV trial did not explore the impact of ACEi on measures of pulmonary vascular health. We hypothesised that infants enrolled in the ISV trial who received enalapril would have lower mean PA pressure compared to those who received placebo.

Materials and methods

The ISV trial was a double-blind, randomised controlled trial comparing enalapril versus placebo amongst infants with a functional single ventricle. The study enrolled infants at 10 centres in the United States of America and Canada from August 2003, to May 2007. The primary outcome was age for weight-for-age z score at 14 months of age. Inclusion criteria were infants with single-ventricle physiology between 1 week and 45 days of age with stable systemic and pulmonary blood flow in whom a superior cavopulmonary connection was planned. Patients who were < 35 weeks gestational age, small for gestational age (<10% percentile), had a known chromosomal or phenotypic syndrome associated with growth failure or known contraindications to ACEi were excluded. The ISV trial design, methods, and main results have been previously published.[20,21] We applied for and obtained the ISV trial database from the PHN. The University of Alberta Health Research Ethics Board waived the need for full review given the publicly available nature of this dataset.

The trial protocol included collecting haemodynamic and angiographic data from all clinically indicated cardiac catheterisations performed prior to SCPC. A study visit was performed 7 days after the SCPC including oxygen saturation determination. The primary outcome of our analysis was invasively measured mean PA pressure at the time of the pre-SCPC catheterisation. If the mean PA pressure was not recorded in the catheterisation dataset, a pulmonary venous wedge pressure was taken as a representative of mean PA pressure if <18 mmHg.[22] Transpulmonary gradient and pulmonary-to-systemic blood flow ratio recorded during pre-SCPC catheterisation and oxygen saturation post-SCPC (7 days after surgery) were secondary outcomes.

The following catheterisation data were extracted from the PHN dataset: age at the time of catheterisation, type of anaesthesia during catheterisation, ventricular morphology, and type of shunt (right ventricle to pulmonary artery versus aortopulmonary). Central shunt and Blalock–Taussig shunt were grouped together as an aortopulmonary shunt.

The initial enalapril dose prescribed in the ISV trial was 0.1 mg/kg/day. The dose was uptitrated as tolerated over a period of 2 weeks to the target dose of 0.4 mg/kg/day, given in two divided doses per day. The dose of the study drug was then adjusted for weight gain at each study visit. The cumulative dose of enalapril from the time of the first dose until pre-SCPC catheterisation data was extracted from the pharmacy dispensing dataset. The study drug temporary stop and restart dataset was queried to determine the total duration of enalapril exposure prior to catheterisation in days. The cumulative enalapril dose (mg/kg) was calculated by multiplying the mean dose received (mg/kg/day) by the total duration of exposure in days; the latter was calculated by subtracting the age at the time of the first dose from the age at the time of catheterisation. Patients on enalapril were grouped into low- and high dose, based on a cut-off of 0.3 mg/kg/day.

Independent sample Student's t-test or Wilcoxon rank-sum test was used to compare the enalapril versus placebo groups. The relationship between cumulative enalapril dose and PA pressure was assessed using Pearson's correlation. The results were considered statistically significant at a p-value < 0.05. Data analysis was performed using SAS software v. 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Study population

Within the ISV trial, 179 of 230 patients underwent pre-SCPC cardiac catheterization and were included in the current analysis. There were 94 patients (53%) in the placebo group and 85 (47%) in the enalapril group. Baseline patient characteristics were similar between the two groups (Table 1). Mean PA pressure measurements were not available in 20 patients, 8 (9%) in the enalapril group and 12 (13%) in placebo group. There were no patients who withdrew from the placebo group. In the enalapril group, four patients (5%) withdrew from the study prior to catheterisation. The reasons for withdrawal were sepsis, parental refusal, initiation of captopril rather than enalapril and in one patient, no reason was provided. The mean enalapril dose was 0.3 ± 0.1 mg/kg/day and the duration of exposure to enalapril was 108 ± 52 days. There were 53 patients (62%) who were on high-dose enalapril (0.3–0.4 mg/kg/day) at the time of pre-SCPC catheterisation.

Haemodynamic outcomes

The primary analysis showed no difference in the mean PA pressure between the enalapril and placebo groups (13.1 ± 2.9 versus 13.7 ± 3.4 mmHg, p = 0.31). Secondary outcome variables also did not differ between study groups (Table 2).

Pre-specified subgroup analysis was performed according to the morphology of the ventricle. There was no difference in the enalapril versus placebo groups for any of the outcome measures. Within the group with right ventricular morphology (Table 3), the mean PA pressure was 13.0 ± 2.8 (enalapril) compared to 13.7 ± 3.6 (placebo) (p = 0.17). In patients with left ventricle morphology, the mean PA pressure was 14.0 ± 3.5 versus 13.3 ± 2.9 in the enalapril and placebo groups, respectively (p = 0.68).

Pre-specified subgroup analysis was also performed according to the type of shunt. In infants who had a Sano shunt (Table 4), the mean PA pressure was 13.0 ± 2.5 in the enalapril group versus 14.0 ± 3.6 in the placebo group (p = 0.25). In the Sano shunt patients, the post-SCPC oxygen saturation was 84 ± 4% in the enalapril group versus 82 ± 5% in the placebo group (p = 0.007). In infants who received an aortopulmonary shunt, the mean PA pressure was 14.0 ± 3.2 in the enalapril group versus 14.0 ± 3.4 in the placebo group (p = 0.75), and post-SCPC oxygen saturation was similar in the enalapril and placebo groups (83 ± 6 versus 82 ± 6, respectively, p = 0.96).

Impact of high-dose enalapril

The mean PA pressure was 13.2 ± 3.6 in the high-dose enalapril group (0.3–0.4 mg/kg/day) versus 13.2 ± 3.5 in the low-dose group (0.1–0.2 mg/kg/day) (p = 0.98). Correlation analysis showed no correlation between cumulative enalapril dose and PA pressure (r = -0.042, p-value = 0.72) (Fig 1).

Discussion

This is an exploratory study on the role of ACEi in pulmonary vascular remodelling in infants with single-ventricle physiology. Using the Pediatric Heart Network ISV dataset, we found no

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Table 1. Baseline characteristics

Characteristic	Enalapril (n = 85)	Placebo (n = 94)	p value
Mean age at the time of catheterisation in days (± SD)	139 ± 48	140 ± 49	0.53
General anaesthesia	54 (64)	48 (51)	0.42
Conscious sedation	31 (36)	46 (49)	0.38
Pulmonary artery pressure not available*	8 (9)	12 (13)	0.64
Right ventricle morphology	69 (81)	80 (85)	0.36
Norwood with aortopulmonary shunt	41 (48)	49 (52)	0.18
Norwood with Sano shunt	34 (40)	39 (41)	0.35
Other palliation (PAB, DKS)	10 (12)	6 (6)	0.28
Mean dose of enalapril (mg/kg/day) (± SD)	0.3 ± 0.1	N/A	0.14
Mean duration of enalapril (± SD)	108 ± 52	N/A	0.32

Results are provided as n (%) unless otherwise specified.
DKS = Damus–Kaye–Stansel; PAB = pulmonary artery band; SD = standard deviation.
*No direct measurement of pulmonary artery pressure and pulmonary vein wedge pressure > 18 mmHg.

Table 2. Primary and secondary outcomes

Characteristic	Enalapril (n = 85)	Placebo (n = 94)	p value
Mean pulmonary artery pressure (mmHg)	13.1 ± 2.9	13.7 ± 3.4	0.31
Transpulmonary gradient (mmHg)	6.7 ± 2.5	6.9 ± 3.2	0.59
Pulmonary-to-systemic blood flow ratio	1.1 ± 0.5	1.0 ± 0.5	0.43
Oxygen saturation post-SCPC surgery (%)	83.1 ± 5.0	82.2 ± 5.3	0.26

Results are provided as mean ± SD.
SCPC = superior cavopulmonary connection.

Table 3. Primary and secondary outcomes according to right (n = 149) and left (n = 30) ventricle morphology

Characteristic	Enalapril (n = 85)	Placebo (n = 94)	p value
Mean pulmonary artery pressure (mmHg)	**13.0 ± 2.8**	**13.7 ± 3.6**	**0.17**
	14.0 ± 3.5	13.3 ± 2.9	0.68
Transpulmonary gradient (mmHg)	**6.6 ± 2.6**	**7.1 ± 3.4**	**0.37**
	7.2 ± 2.0	6.0 ± 2.3	0.28
Qp:Qs ratio	**1.1 ± 0.4**	**1.1 ± 0.6**	**0.73**
	1.2 ± 0.8	1.0 ± 0.2	0.42
Oxygen saturation post-SCPC surgery (%)	**82 ± 5**	**82 ± 5**	**0.21**
	82 ± 4	82 ± 6	0.76

Results are provided as mean ± SD.
Right ventricle = bold font; SCPC = superior cavopulmonary connection.

Table 4. Primary and secondary outcomes in infants with Sano shunt (n = 73) and aortopulmonary shunt (n = 90)

Characteristic	Enalapril (n = 75)	Placebo (n = 88)	p value
Mean pulmonary artery pressure (mmHg)	**13.0 ± 2.5**	**14.0 ± 3.6**	**0.25**
	14.0 ± 3.2	14.0 ± 3.4	0.75
Transpulmonary gradient (mmHg)	**7.0 ± 2.7**	**7.3 ± 3.4**	**0.37**
	7.0 ± 2.3	7.0 ± 3.0	0.31
Qp:Qs ratio	**1.0 ± 0.4**	**1.0 ± 0.5**	**0.52**
	1.2 ± 0.5	1.1 ± 0.5	0.97
Oxygen saturation post-SCPC surgery (%)	**84 ± 4**	**82 ± 5**	**0.007**
	83 ± 6	82 ± 6	0.96

Results are provided as mean ± SD.
Sano shunt = bold font; SCPC = superior cavopulmonary connection.

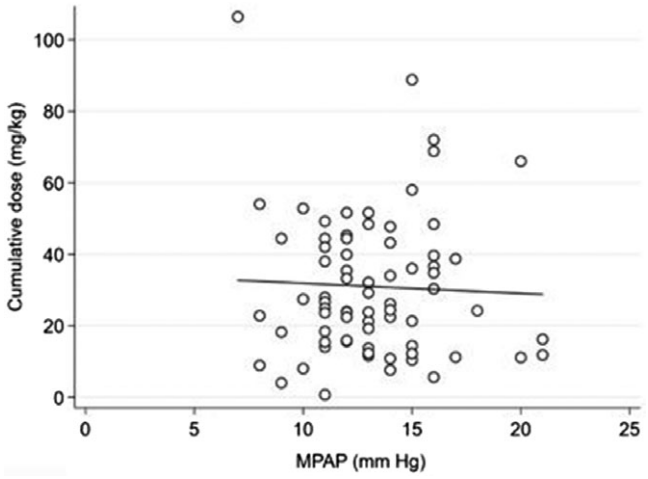

Figure 1. Correlation analysis: Cumulative enalapril dose (mg/kg) amongst infants in the enalapril group versus mean pulmonary artery pressure.

difference in mean PA pressure, transpulmonary gradient, or pulmonary-to-systemic blood flow ratio at the time of pre-SCPC catheterisation, and no difference in oxygen saturation post-SCPC surgery between enalapril and placebo groups. In the pre-specified subgroup analysis of those with a Sano shunt, we observed a higher (yet clinically marginal) post-SCPC saturation in infants who received enalapril. Infants who received high-dose enalapril had similar PA pressure compared to infants who received low-dose enalapril.

These negative findings may be due to the complex pathogenesis of pulmonary vascular remodelling in infants with single-ventricle CHD, limitations of the available dataset, and/or that enalapril is simply not an effective pulmonary vasodilator in this population. Animal models exploring the role of ACEi in the pathophysiology of pulmonary hypertension may not reflect the complex pathophysiology seen in infants with SV-CHD.[23] In the study by Zhao et al,[3] the animal model of hypoxia-induced pulmonary hypertension did not take into account the pressure and flow components that contribute to pulmonary vascular remodelling in infants with SV-CHD.[24] Furthermore, the conversion of the prodrug enalapril to the active moiety enalaprilat is potentially more effective in rats as they express carboxylesterases in both plasma

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and liver, in contrast to humans in whom this occurs mainly in the liver.[25] To our knowledge, no data are available on the expression of ACE in healthy human neonatal lungs, though data on the expression of lung ACE in the developing pulmonary arteries of a rat model suggests that by term, all vessels expressed ACE[26] and could play a role in pathologic pulmonary vascular remodelling. There are several other pathways that have been reported to contribute to pulmonary vascular remodelling, i.e., endothelin, oxidative injury, and shear stress,[27–29] but these were not tested in the ISV trial.

Infants in the ISV trial were haemodynamically stable at the time of enrolment and had a controlled source of pulmonary blood flow. It is theoretically possible that the genotype expression of the ACE in these patients may not be similar to those who have unstable haemodynamics and are potentially more susceptible to injury in the pulmonary vascular bed. Previous data from the ISV trial showed that certain ACE genotypes are associated with reverse myocardial remodelling after SCPC surgery.[30] However, the impact on pulmonary artery pressure was not explored in this study.

Another explanation for the negative findings of our study may be an inadequate exposure to enalapril (on average less than 4 months in the study cohort). A longer exposure to an ACEi may be needed to detect changes in PA pressure and PVR using the currently available clinic tools. Several studies in adult Fontan patients have demonstrated that changes at the histological and molecular levels may start before any clinical changes are evident.[1,31,32] Inter-individual differences in enalaprilat exposure due to individual variations in enalapril pharmacokinetics may have contributed to the results as well.[33,34]

We found that infants with a Sano shunt who received enalapril had a higher oxygen saturation post-SCPC surgery. However, the difference was small and clinically marginal. A possible explanation for this finding could be the differential expression of ACE in the lungs between patients with a Sano versus aortopulmonary shunt. In animal models of aortopulmonary shunt-induced pulmonary hypertension, the use of ACEi resulted in lower pulmonary vascular resistance and arteriolar thickness compared to placebo.[5] However, no prior clinical or animal data exist regarding the impact of ACE inhibition in the context of a Sano shunt, and this finding remains difficult to explain. Alternatively, this may reflect a type 1 error related to multiple statistical comparisons.

Study limitations

Our data source, the Pediatric Heart Network ISV trial, provides the best available data to explore our hypothesis given the relatively large number of patients enrolled and the systematic nature of data collection. However, the initial study was not powered to detect a difference in mean PA pressure between enalapril or placebo groups. Planning a randomised trial to detect this difference would be difficult. Using the current data with the effect size of mean PA pressure (13.7 mmHg in enalapril group versus 13.1 mmHg in the placebo group, $\alpha = 0.05$, 80% power), a total of 393 patients would be required in each arm to demonstrate a difference in mean PA pressure. This is likely not feasible given the initial challenges the ISV trial faced.[35]

The pre-SCPC catheterisation dataset also has some limitations. A pre-SCPC catheterisation was not required as per the ISV study protocol. The baseline conditions during the cardiac catheterisation were not pre-specified and some patients were under general anaesthesia while others received conscious sedation, which may have a differential impact on haemodynamics. In addition, some parameters (i.e., haemoglobin, oxygen consumption, and partial pressure of oxygen) were not available to calculate systemic and pulmonary vascular resistance. Although mean PA pressure is an important haemodynamic aspect in single-ventricle physiology, the ideal primary outcome from catheterisation data would be pulmonary vascular resistance as PA pressure is also influenced by pulmonary blood flow and ventricular compliance and not solely pulmonary vascular resistance. Not all patients had a direct measurement of PA pressure, and therefore we used pulmonary venous wedge pressure (if < 18 mmHg) as a surrogate for mean PA pressure. Several anatomical factors can also influence pre-SCPC haemodynamics including branch pulmonary artery stenosis and coarctation of the aorta, for which data were not available for all patients.

In conclusion, this retrospective analysis of the ISV dataset demonstrates that the short-term use of enalapril in infants with a single-ventricle palliation did not impact pre-SCPC haemodynamics. The pathophysiology of pulmonary vascular remodelling in these infants is complex, and this study suggests that enalapril plays no role in that process in this population.

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Conflicts of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (Tri-Council Policy Statement, Government of Canada) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the Health Research Ethics Board of the University of Alberta.

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