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3-Month *Enalapril* Treatment in Pediatric Fontan Patients With Moderate to Good Systolic Ventricular Function



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Many Fontan patients with and without systolic ventricular dysfunction are being treated with angiotensin-converting enzyme (ACE) inhibitors, despite its effectiveness remaining unclear. In the present study, we evaluated the short-term effect of enalapril on exercise capacity, vascular and ventricular function in pediatric Fontan patients with moderate-good systolic ventricular function. Fontan patients between 8 and 18 years with moderate-good systolic ventricular function and without previous ACE inhibitor treatment were included and were treated with enalapril for 3 months. During the first 2 weeks, the dosage was titrated according to systolic blood pressure (SBP). Exercise tests, ventricular function assessed by echocardiography, arterial stiffness measurements, and plasma levels of N-terminal pro-B-type natriuretic peptide assessed before and after a 3-month enalapril treatment period was compared. A total of 28 Fontan patients (median age 13.9 years, 6 to 15 years after Fontan operation) completed the study with a mean dosage of 0.3 ± 0.1 mg/kg/d. A total of 6 patients (21%) experienced a significant drop in SBP and 6 others (21%) experienced other adverse events. Enalapril treatment lowered the SBP (from 110 to 104 mmHg, $p = 0.003$) and levels of N-terminal pro-B-type natriuretic peptide (from 80 to 72 ng/L, $p = 0.036$). However, enalapril treatment did not improve exercise capacity, ventricular function, or arterial stiffness. In conclusion, short-term ACE inhibition has no beneficial effect in Fontan patients with moderate-good systolic ventricular function. © 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) (Am J Cardiol 2022;163:98–103)

Although survival of Fontan patients has improved, life expectancy is still less than normal, and many patients suffer from morbidities. Exercise performance, diastolic and systolic ventricular function are already reduced at a young age.^{1,2} Because severe diastolic and systolic dysfunction may not be present yet, both functions deteriorate over time in these patients, which may eventually result in heart failure.^{1,2} In patients with biventricular heart circulation, angiotensin-converting enzyme (ACE) inhibitors have become the cornerstone of systolic heart failure treatment as they have been shown to improve exercise performance, diastolic and systolic ventricular function, and decrease systemic vascular resistance in adult and pediatric patients

with mild to severe systolic heart failure.^{3–10} Because its effectiveness in biventricular heart patients, many Fontan patients are currently treated with ACE inhibitors, including those without overt systolic ventricular dysfunction, despite the lack of evidence of its efficacy in this patient population.^{11,12} Therefore, in this study we evaluated the effect of ACE inhibition in pediatric Fontan patients with moderate-good systolic ventricular function and hypothesized that it may improve exercise performance and ventricular and vascular function. Additionally, adverse events and tolerability were evaluated.

Methods

Fontan patients from 8 to 18 years old who were operated at the Leiden University Medical Center were recruited from July 2017 to October 2019. Patients with pre-existent ACE inhibitor use and those unable to exercise were excluded. Written informed consent was obtained from all participants or their parents or guardians. The study was approved by the Medical Ethical Committee Leiden-Den Haag-Delft.

For this study patients were treated with enalapril, an ACE inhibitor, for 3 months. This period was chosen as previous studies have shown beneficial effects of ACE inhibitors within 12 weeks of treatment, especially on exercise

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capacity, the primary end point of this study.^{3,5,13,14} Initial enalapril dosage was 5 mg/day and was titrated, as tolerated, to the target dose of 0.5 mg/kg/day or a maximum of 20 mg/day. Enalapril dosage was titrated by blood pressure measured weekly for at least 2 weeks after initiation of treatment. If systolic blood pressure (SBP) fell >20%, or if patients experienced side effects, the dosage was lowered. Renal function (urea and creatinine blood levels) was assessed at baseline, after 2 weeks of treatment with the maximal tolerated dosage, and at the end of the study. At baseline patients were asked if they were familiar with syncope, dizziness, low blood pressure, or if they experienced other complaints, such as palpitations. During the titration period and after 3 months of treatment, patients were asked about it again. At baseline, and after 3 months of treatment, a cardiopulmonary exercise test, echocardiography, arterial stiffness measurement, and blood sample were performed, as described later.

Exercise testing was performed on an upright bicycle ergometer (Jaeger ER 900; Viasys Healthcare, Höchberg, Germany) with breath-by-breath analysis using a flowmeter (Triple V volume transducer) and computerized gas analyzer (Jaeger Oxycon Champion, Viasys Healthcare or Carefusion Vyntus, Vyair Medical). Starting wattage and workload increment per minute were determined by the age of the patient. Patients were encouraged to exercise until exhaustion. Tests were considered maximally performed when the peak respiratory exchange ratio was ≥ 1.0 . Maximal exercise parameters were only assessed in patients with a maximal test. Peak work rate, heart rate at peak, peak oxygen uptake ($\text{VO}_{2\text{ peak}}$), $\text{VO}_{2\text{ peak}}$ per heartbeat, the respiratory minute to CO_2 production slope (VE/VCO_2), and the oxygen uptake efficiency slope were derived from the exercise test following previously published methods.¹⁵

Transthoracic echocardiography was performed on a Vivid S6/S60 ultrasound machine (General Electric Healthcare, Norway). Images were stored and analyzed offline using EchoPac (version 203, GE Healthcare, Little Chalfont, United Kingdom). Measurements of 3 consecutive cardiac cycles were averaged for analysis. Pulse wave Doppler recordings were performed across the atrioventricular valve to assess early and late diastolic velocities and calculate the ratio of those velocities (E/A). Through Tissue Doppler imaging, myocardial velocity curves from the basal part of the single ventricles' lateral wall and ventricular septum were obtained to assess peak systolic and peak early and late diastolic velocities. Furthermore, the ratio between the pulse wave and tissue Doppler peak early diastolic velocities (E/E') of the lateral wall was calculated. Longitudinal global peak strain, evaluating systolic performance, was obtained from the dominant ventricle using speckle-tracking strain analysis from the 4-chamber apical view as previously described.¹⁶ To assess global longitudinal strain, at least 5 of 6 segments had to show acceptable curves. Furthermore, if the ventricular septum defect was larger than 1 segment, the strain was conducted from both lateral walls.

The oscillometric arteriograph device (Tensiomed, Budapest, Hungary) was used to measure pulse wave velocity of the aorta, augmentation index of the aorta, and central SBP. Measurements were performed in a supine position

with the cuff on the left arm. The arteriograph software calculates average values and determines the accuracy of the measurement with an SD. Since automatic calculation was not always possible because of small pulse waves or movement, we analyzed each cardiac cycle individually using the software. Measurements were considered valid after a visual check and when a reliable value could be calculated with an SD of the pulse wave velocity of the aorta <1.0 m/s.

From a venous puncture plasma creatinine, urea, and N-terminal pro-B-type natriuretic peptide (NT-pro BNP) levels were assessed.

Data analysis was performed using SPSS Statistics software (Version 25.0 IBM SPSS, New York, United States).

Variables were tested for normality with histograms and QQ-plots. Continuous data are reported as mean $\pm$ SD or as median with first to third quartile (Q1-Q3) in case of non-normality. Categorical data are presented as a number with percentages. A paired sample *t* test or a Wilcoxon signed-rank test for non-normal distributed values were used for comparison between pre-enalapril and follow-up measurements. A $p < 0.05$ was considered significant. The primary end point for this study was exercise performance and specifically the $\text{VO}_{2\text{ peak}}$. Using Cohen's *D* of 0.49 as effect size, calculated with mean and SD from previously published data,¹⁷ an alpha of 0.05% and 80% power, we calculated that 35 subjects would be sufficient to detect a 10% increase in $\text{VO}_{2\text{ peak}}$.

Results

A total of 74 Fontan patients were eligible for inclusion, of which 36 agreed to participate (49%). Patients who participated did not differ from those who did not in terms of age (median of 14.0 years [12.7 to 16.6] for participants vs 13.0 years [11.7 to 16.0] for nonparticipants, $p = 0.364$) and morphology of the main single ventricle ($p = 0.374$). As only 6 patients participated in the baseline measurements, a total of 30 patients were enrolled in this study and started with enalapril treatment. During the study 1 patient withdrew at the request of parents and 1 patient was excluded for further analysis because of medication noncompliance. The remaining 28 patients completed the study of whom baseline characteristics are summarized in Table 1. Initial diagnosis and ventricular morphology differed in the group.

An overview of blood pressure measurements and plasma urea and creatinine levels is shown in Table 2. SBP was significantly lower during the study as compared with baseline. Plasma levels of urea and creatinine did not change significantly. Eleven patients could not reach the targeted dosage because of a decrease in SBP ($n = 6$, 21%) or other adverse events, consisting of syncope ($n = 2$), dizziness ($n = 2$), and palpitations ($n = 1$). Furthermore, 1 patient reported a hacking cough after completion of the study which disappeared after discontinuation of enalapril. This means that 21% of the patients experienced adverse events other than the predetermined drop in SBP, which was higher when compared with baseline where 2 patients (7.1%) reported that they were familiar with syncope ($n = 2$) and palpitations ($n = 1$). All patients completed the study with a mean dosage of 0.29 ± 0.1 mg/kg/day, dosages ranging from 5 to 20 mg/day.

Table 1
Patient Characteristics of the study population

Characteristics	n = 28
Age (years)	13.9 [13.0-16.7]
Males	18 (64%)
Height (cm)	164.1 (12.5)
Weight (kg)	53.3 (12.6)
BSA (m ²)	1.57 (0.2)
Oxygen saturation (%)	95.6 (2.1)
Diagnosis	
Tricuspid atresia	6 (21%)
Pulmonary atresia	1 (4%)
Double inlet left ventricle	4 (14%)
Double outlet right ventricle	1 (4%)
Hypoplastic left heart syndrome	8 (29%)
Unbalanced atrioventricular septal defect	4 (14%)
Other	4 (14%)
Main ventricle	
Left	13 (46%)
Right	12 (43%)
Undifferentiated	3 (11%)
Age at Glenn operation (years)	0.5 [0.37-0.75]
Age at Fontan operation (years)	3.1 (0.6)
Type Fontan tunnel	
TCPC-EC	28 (100%)
Initial Fenestration	26 (92%)
Open	1 (4%)
Closed (naturally or by device)	25 (96%)

Data expressed as n (%), mean ($\pm$ SD), and median [Q1-Q3].

BSA = body surface area; TCPC-EC = total cavopulmonary connection with an extracardiac conduit.

Results of the exercise tests are shown in Table 3. A total of 3 patients (11%) were not able to achieve a respiratory exchange ratio ≥ 1.0 and were excluded for comparison of the maximal exercise parameters. The Fontan patients showed on average a low exercise capacity at baseline, reflected by a low $\text{VO}_{2\text{ peak}}$ and high VE/VCO_2 slope. A 3-month treatment with enalapril did not improve any of the exercise parameters.

Table 4 depicts the results of the cardiac and vascular function. On echocardiography, all patients showed a subjective moderate to good systolic ventricular function. At baseline, Tissue Doppler peak systolic velocities were decreased and global peak longitudinal strain was similar compared with normal controls as was already reported in a previous study.¹⁸ Diastolic ventricular function was

Table 3
Cardiopulmonary exercise test results

	Pre-enalapril	Enalapril	P-value
Maximal exercise (n=25)			
RER_{peak}	1.13 (0.08)	1.12 (0.07)	0.383
WR_{peak} (watt)	120.4 (36.3)	123.0 (38.8)	0.261
HR_{peak} (bpm)	172.8 [164-184]	173.6 [164-185]	0.637
$\text{VO}_{2\text{peak}}$ (ml/kg/min)	26.2 (4.7)	26.7 (6.5)	0.691
Peak O_2 pulse (ml/beat)	8.53 (1.6)	8.56 (2.1)	0.900
Submaximal exercise (n=28)			
VE/VCO_2 slope	36.1 [32.6-40.8]	38.1 [34.1-42.5]	0.133
OUES/kg	27.2 (6.0)	26.9 (6.5)	0.706

Data expressed as mean (SD) or median [IQR].

HR_{peak} = maximal heart rate at peak exercise; RER_{peak} = respiratory exchange ratio at peak exercise; OUES = oxygen uptake efficiency slope; Peak O_2 pulse = maximal oxygen uptake per heartbeat; VE/VCO_2 slope = slope of respiratory minute to CO_2 production; $\text{VO}_{2\text{peak}}$ = peak oxygen uptake; WR_{peak} = maximum work rate achieved.

decreased at baseline as well, with a low E/A ratio and high E/E' ratio, compared with normal controls from our previous published data. Furthermore, atrioventricular valve regurgitation was moderate in 6 and mild in 11 patients. (Neo)Aortic valve regurgitation was moderate in 3 and mild in 2 patients. All echocardiographic parameters, systolic and diastolic, did not change with enalapril treatment. The level of NT-pro BNP, although already low at baseline, decreased significantly after treatment with enalapril. Central SBP significantly decreased. Although the values of the augmentation index of the aorta tended to decrease, this did not reach the threshold for statistical significance. Pulse wave velocity of the aorta showed no difference either.

Discussion

Our study evaluating the effect of a 3-month enalapril treatment in pediatric Fontan patients demonstrated no improvement of exercise capacity nor systolic and diastolic ventricular function, and arterial stiffness. SBP and NT-pro-BNP levels, however, did reduce slightly. Nonetheless, a large proportion of patients had significant side effects.

ACE inhibition has been the cornerstone of the treatment of congestive heart failure in adult patients.

Table 2
Systolic blood pressure and plasma urea and creatinine levels during trial

	Week 1 Baseline	Week 2 Control BP 1	Week 3 Control BP 2	Week 5-6 Control plasma urea and creatinine	3 Months Follow-up
Systolic BP (mmHg)	120.4 (9.2)	109.9* (12.5)	111.0 [†] [99-119]		117.7 [†] (10.2)
Δ SBP from start (%)		-8.6 (10.2)	-7.3 (9.2)		
Creatinine (umol/L)	62.5 [56-68]			64.5 [501-73]	63.0 [58-72]
Urea (mmol/L)	5.3 ($\pm$ 1.1)			5.7 ($\pm$ 1.5)	5.2 [4.5-6.38]

* P-value <0.05 for difference between control and follow-up measurement vs pre-enalapril values.

[†] P-value <0.01.

Data is presented as mean ($\pm$ standard deviation) or median [Q1-Q3].

BP = blood pressure; SBP = systolic blood pressure.

Table 4
Comparison of cardiac and vascular function (n = 28)

	Baseline	Follow-up	P-value
Heart rate (bpm)	63.8 [60.0-82.3]	75.2 [55.0-85.7]	0.387
Cardiac function			
NT-Pro BNP (ng/L)	80.2 [48.4-146.8]	71.5 [42.1-136.4]	0.036
Systolic			
TDI septal S' (m/s)	0.043 [0.03-0.05]	0.043 [0.04-0.05]	0.857
TDI lateral free wall S' (m/s)	0.056 (0.02)	0.055 (0.01)	0.780
Global longitudinal strain (%)	15.3 (3.5)	14.6 (0.6)	0.139
Diastolic			
E (m/s)	0.58 [0.5-0.8]	0.64 [0.6-0.7]	0.819
A (m/s)	0.48 [0.3-0.6]	0.43 [0.4-0.5]	0.106
E/A	1.43 [1.1-1.9]	1.51 [1.2-1.9]	0.361
TDI septal E' (m/s)	0.070 [0.05-0.09]	0.073 [0.06-0.09]	0.454
TDI septal A' (m/s)	0.041 (0.02)	0.043 (0.02)	0.430
TDI lateral free wall E' (m/s)	0.083 (0.03)	0.078 (0.03)	0.379
TDI lateral free wall A' (m/s)	0.037 [0.03-0.06]	0.042 [0.03-0.05]	0.931
E/E'	8.8 [6.7-11.9]	7.7 [7.3-11.7]	0.864
Vascular function			
Central SBP (mmHg)	109.9 (9.6)	104.3 (9.2)	0.003
PWVao (m/s)	5.31 (0.9)	5.17 (1.2)	0.502
AIXao (%)	19.4 (9.7)	17.0 (9.8)	0.062

Data expressed as mean (SD) or median [IQR].

A = peak late diastolic velocity; A' = peak late diastolic TDI velocity; AIXao = augmentation index of the aorta; E = peak early diastolic velocity; E' = peak early diastolic TDI velocity; Global longitudinal strain = global longitudinal strain from the four-chamber apical view; NT-pro BNP = N-terminal pro brain natriuretic peptide; PWVao = pulse wave velocity of the aorta; S' = peak systolic TDI velocity; SBP = systolic blood pressure; TDI = Tissue Doppler imaging.

Studies have shown beneficial effects of enalapril in patients with reduced ejection fraction with dosages ranging from 2.5 to 40 mg/day.^{3,7-10} Interestingly, some of these studies found no relation between the dose of enalapril and clinical outcome.^{9,10} However, the role of ACE inhibition in patients with diastolic heart failure with preserved ejection fraction is unknown as a recent meta-analysis showed that randomized trials have not demonstrated a survival benefit of ACE inhibitors in these patients.¹⁹ In pediatric patients with acquired and congenital heart disease associated with congestive heart failure and patients with a volume-overloaded biventricular circulation, enalapril dosages between 0.15 and 0.5 mg/kg/day have been effective.^{4,6,14,20} In the present study, we aimed for a maximal enalapril dose of 0.5 mg/kg/day with a maximum of 20 mg. The dosage reached after the introduction phase ranged from 5 to 20 mg/day with a mean of 0.29 ± 0.1 mg/kg/day, which correlates well with pediatric and adult dosages presented in the literature.

ACE inhibitors are frequently used in Fontan patients. In 2 previous observational studies, 36% and 57% of the Fontan patients were treated with ACE inhibitors.^{11,12} In the study by Anderson et al¹¹ the use of ACE inhibitors in pediatric Fontan patients correlated with severe atrioventricular valve regurgitation and right ventricular morphology but

not with the presence of ventricular dysfunction. In fact, in the study by Wilson et al¹² 2/3 of the patients receiving enalapril did not have systolic ventricular dysfunction indicating that in most Fontan patients ACE inhibitors are prescribed as a preventive therapy, although proof of effectiveness is lacking. In this study, we showed that a 3-month enalapril treatment had no demonstrable impact on exercise capacity, nor on systolic or diastolic function in pediatric Fontan patients with moderate-good systolic ventricular function.

We did find a reduction in blood pressure and levels of NT-pro-BNP after a 3-month enalapril treatment. The effect on blood pressure might implicate a reduction in vascular resistance. However, both aortic stiffness parameters, including augmentation index and pulse wave velocity, did not change significantly. As both parameters are affected by blood pressure, a small change can be expected based on blood pressure lowering, which does not always indicate that there is a reduction in aortic stiffness. Other retrospective studies were also unable to demonstrate an improvement in endothelial function in pediatric Fontan patients during treatment with ACE inhibitors.^{21,22} We did find a slight decrease in NT-pro-BNP levels which suggests improved filling pressures. Although E/E' did not change, there may have been an effect on filling pressures, which were not measured in this study. A small catheterization study reported a reduction of elevated filling pressures after enalapril treatment in patients with univentricular hearts, either before or after Fontan completion, suggesting an improvement of diastolic function.²³ Another positive effect of enalapril might be the preservation of renal function in Fontan patients as previously shown in a retrospective study.²⁴

Two previous studies have prospectively evaluated the effect of enalapril in 10 and 18 pediatric Fontan patients, respectively.^{25,26} Both showed that no parameter, including vascular resistance, cardiac index at rest, diastolic and systolic ventricular function, exercise capacity, and cardiac autonomous nervous activity improved after a 3 to 6-month enalapril treatment period; these results are comparable with ours. Although no effect on functional outcome was observed after several months of treatment, long-term enalapril treatment could have a beneficial effect. A previous study with enalapril in biventricular patients with congestive heart failure showed that survival curves did not separate until 18 months of treatment.⁸ Long-term beneficial effects on ventricular failure may be because of the inhibition of the cardiac renin-angiotensin-aldosterone system (RAAS), thereby limiting cardiac remodeling and cardiomyocyte fibrosis.²⁷ High levels of renin and aldosterone can be found in adult patients with congenital heart disease, including patients with single-ventricle physiology.²⁸ Furthermore, levels of renin and aldosterone have been shown to correlate with symptom severity and ventricular dysfunction in these patients²⁸ and therefore RAAS activation may play a role in the deterioration of the Fontan circulation. However, if long-term treatment with ACE inhibition or other RAAS inhibition may have beneficial effects in Fontan patients warrants further investigation.

Our study showed that a large proportion of patients experienced a significant adverse event which may raise

concerns regarding how well ACE inhibition is tolerated by this patient cohort. Lowering blood pressure in a chronic volume unloaded circulation with limited preload reserve, because of the lack of a subpulmonary ventricle, is likely to cause negative effects. Because of the limited or even absent preload reserve, afterload reduction will not lead to increased cardiac output as typically seen in biventricular circulations, but in a Fontan circulation may even cause a decrease in cardiac output which could be detrimental.²⁹ One previous small study in pediatric Fontan patients has shown a lower increase in cardiac index during exercise after treatment with enalapril.²⁵

Because many Fontan patients are treated with ACE inhibitors, the ventricular function must be severely impaired to limit cardiac output in a Fontan circulation.²⁹ Preload has been recognized as one of the main limiting factors of cardiac output increase in Fontan patients, of which pulmonary vascular resistance is one of the main contributors. Because low pulmonary vascular resistance is a prerequisite for a functioning Fontan circulation, pulmonary vasodilators have emerged as a promising medical therapy in the prevention of Fontan failure. The effect of pulmonary vasodilators in Fontan patients has already been investigated in a few large randomized studies and showed an increase in VO_2 peak of 3% to 5% after treatment.³⁰

This study has some limitations. Our study includes a small sample size, with the predefined recruitment target not being reached despite many eligible participants. Nonetheless, it is the largest prospective study of enalapril in Fontan patients yet, and the power to conclude that enalapril has no beneficial effect was enhanced by lower-than-expected variance. Although the underlying cardiovascular defects were heterogeneous as in other Fontan studies, our sample was relatively homogenous as only pediatric patients with extracardiac conduit and moderate-good systolic ventricular function were included. We did not study the effect of ACE inhibition in Fontan patients with significant ventricular dysfunction. The treatment period chosen could have been too short, however, the treatment period was chosen based on previous studies which showed a beneficial effect on exercise parameters within 4 to 12 weeks after initiating treatment with ACE inhibitors, which was the primary end point of interest.^{3,5,13,14} Lastly, echocardiography has its limitations in assessing diastolic function or ventricular dimensions. However, both cardiac catheterization and MRI would have increased the burden in the present study because repeated measurements were necessary.

In conclusion, our study demonstrated that a 3-month enalapril treatment period in pediatric Fontan patients with moderate-good systolic ventricular function does not enhance exercise capacity or improve vascular and echocardiographic ventricular function. Enalapril, however, did reduce SBP and NT-pro BNP levels. Nonetheless, enalapril was not well-tolerated as a large proportion of patients experienced adverse events. Based on these results, we conclude that short-term ACE inhibition has no beneficial effect in Fontan patients with moderate-good systolic ventricular function.

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Disclosures

The authors have no conflicts of interest to declare.

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