Original Article

Improvement of cardiac function in children with congenital heart disease (involving a left-to-right shunt) treated with angiotensin-converting enzyme inhibitor captopril

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Abstract: Objective: This study aimed to analyze the efficacy of captopril in children with congenital heart disease (CHD) involving a left-to-right shunt. Methods: A total of 87 children with CHD involving a left-to-right shunt in our hospital were assigned to two groups by random blind draw method, including 43 cases in Group B received conventional treatment and 44 cases in Group A received captopril. The efficacy of the two groups was then compared. Results: The Group A showed decreased levels of serum BNP, MMP-2 and MMP-9, and increased levels of TIMP-1 compared with the Group B at 3 and 6 months after treatment (P < 0.05). The Group A exhibited decreased Qp/Qs, Tei index and PASP, and increased LVEF compared with Group B at 3 and 6 months after treatment (P < 0.05). Conclusion: Captopril can significantly improve the cardiac function in children with CHD involving a left-to-right shunt, regulate the level of serum indices and prevent development of pulmonary artery hypertension.

Keywords: Children with congenital heart disease, left-to-right shunt, angiotensin-converting enzyme inhibitor, captopril, cardiac function

Introduction

Congenital heart disease (CHD) has the highest prevalence among all possible cardiovascular diseases in children, with the left-to-right shunt as the main type [1]. Clinical findings showed that the risk of pulmonary artery hypertension or congestive heart failure associated with CHD involving a large shunt is significantly increased [2]. Therefore, early treatment of CHD is of great significance for prevention of various concomitant diseases.

Pulmonary artery hypertension in children with CHD typically occurs as a result of increase in pulmonary blood flow and stenosis, contraction, obstruction and injury of pulmonary capillary and pulmonary arteriole, leading to progressive increase of resistance in the pulmonary circuit, which further leads to pulmonary vascular remodeling and causes declined right ventricular function (RVF) [3]. While pulmonary artery hypertension continues to develop to a certain extent, pulmonary vascular obstructive lesion will occur, and children will miss the surgical treatment opportunity. Therefore, how to effectively prevent and reverse pulmonary vascular obstructive lesion is the focus of research in CHD field [4]. Surgical treatment was generally adopted for CHD in the past, but the pediatric patients have lower tolerance to surgery than adults, and there is a higher risk of surgery since children’s body function is still underdeveloped.

Based on this, this study proposed drug therapy at the early stage. Renin-angiotensin system is important and responsible for cardiovascular function regulation [5]. This system is activated in case of CHD involving a left-to-right shunt,
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and the greater the shunt is, the higher the activation degree will be [5]. Angiotensin-converting enzyme inhibitor is considered to be effective in controlling CHD involving a left-to-right shunt and reducing the risk of developing pulmonary artery hypertension and other concomitant diseases. It was found that the levels of SV, LVPS, LVEF, Nt-probNP and cTnI after captopril treatment were all better than those of the control group (P < 0.05) [6]. In addition, the combined treatment with captopril was more effective in improving cardiac function [7]. In this study, 87 children with CHD involving a left-to-right shunt in our hospital were selected to explore the efficacy of captopril and find more effective methods for the clinical treatment of CHD.

Materials and methods

Materials

A total of 87 children with CHD involving a left-to-right shunt in our hospital were assigned to two groups by random blind draw method, including 43 cases in Group B received conventional treatment and 44 cases in Group A received captopril. Children in both groups were aged between 2 months and 2 years. Inclusion criteria: the child who met the diagnostic criteria for CHD [8] and was diagnosed by cardiac ultrasound; who certainly had no pulmonary artery hypertension or other concomitant diseases prior to treatment; with no history of drug allergy; and who had not received any relevant drug treatment. The parent signed the informed consent form for research, and the study was approved by the Ethics Committee of Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science & Technology. Exclusion criteria: the child who manifested any one of the followings: severe coinfection, serum electrolyte disorder, pulmonary artery hypertension, heart failure and CHD involving other shunts were excluded from the study.

Methods

Group B received conventional treatment, and the subjects were administrated with diuretics, digitals and vasodilators. The diuretics adopted was hydrochlorothiazide tablet (specification: 25 mg*100 tablets, GYZZ: H14020796, manufacturer: Shanxi Yunpeng Pharmaceutical Co., Ltd.), given orally at 1-2 mg/kg per dose twice daily. For children who cannot swallow directly, the tablets can be ground into powder mixed with water for feeding. The digitalis adopted was digoxin tablet (specification: 0.25 mg*30 tablets, GYZZ: H31022986, manufacturer: Sino-American Shanghai Squibb Pharmaceuticals Co., Ltd.), given at 0.02-0.03 mg/kg for children aged 2 weeks and younger and 0.03-0.04 mg/kg for children aged 2 weeks to 2 years all in two divided doses. For children who cannot swallow directly, the tablets can be ground into powder mixed with water for feeding. The vasodilator adopted was nitroglycerin. 10 mg of nitroglycerin was mixed in 50 ml of 5% glucose (specification: 1 ml:5 mg, GYZZ: H44020569, manufacturer: Guangzhou Baiyunshan Mingxing Pharmaceutical Co., Ltd.) for intravenous (IV) infusion with a micropump at a rate of 5-10 ml/h. The treatment continued for 8 weeks.

In addition to conventional treatment, Group A was administrated with captopril (Specification: 12.5 mg*20 tablets, GYZZ: H31020678, manufacturer: Sino-American Shanghai Squibb Pharmaceuticals Co., Ltd.), given at 0.5-1.0 mg/kg per dose twice daily. For children who cannot swallow directly, the tablets can be ground into powder mixed with water for feeding. The treatment continued for 8 weeks.

Observed indices

Serum indices: 2 ml of peripheral venous blood was drawn and placed in EDTA anticoagulation tube, which was allowed to stand for half an hour at 4°C and then centrifuged at 3500 rpm for 3 min. Serum after separation was collected by EP tube, and stored at -70°C for testing. The test was completed based on enzyme-linked immunosorbent assay (ELISA). The testing indices included brain natriuretic peptide (BNP), matrix metalloproteinase-2 (MMP-2), tissue inhibitor of metalloproteinase-1 (TIMP-1) and matrix metalloproteinase-9 (MMP-9). Test was conducted before treatment and at 1, 3 and 6 months after treatment, respectively.

Ultrasonic indices: cardiac color Doppler ultrasound scanner together with S5-1 probe was employed, and examination was performed after administration of 30-40 mg/kg chloral hydrate. The indices to be measured included left ventricular ejection fraction (LVEF), pulmonary to systemic blood flow ratio (Qp/Qs), Tei index, pulmonary arterial systolic pressure (PASP).
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LVEF measurement: the left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) were measured in two-chamber and four-chamber views by using modified Simpson’s method. LVEF can then be calculated as the following: \[ \text{LVEF} = \frac{(\text{LVEDV}-\text{LVESV})}{\text{LVEDV}} \] [9].

Qp/Qs measurement: pulmonary blood flow (Qp) and systemic blood flow (Qs) were calculated by Doppler ultrasound equation as the following: \[ \text{blood flow (L/min)} = \frac{(V\times\text{CSA}\times60 \text{ s/min})}{1000 \text{ ml/L}}, \] where V is the mean velocity and CSA is the cross-sectional area of flow [10].

Tei index measurement: by using the tissue Doppler technique, an interval from the end to the onset of tricuspid inflow (a) was recorded in standard apical four-chamber view, and the right ventricular ejection time (b) was measured by recording the anterograde pulmonary blood flow (APBF) from the short-axis view at the base of the heart. Tei index = \( \frac{(a-b)}{b} \) [11].

Pulmonary artery systolic pressure (PASP): the peak velocity of the tricuspid regurgitant frequency spectrum was measured by continuous wave Doppler through the tricuspid valve in apical four-chamber view, and the pressure difference was calculated through Bernoulli equation in fluid dynamics as the following: \[ \text{PASP} = \text{PTR} + \text{PRA} \] [12]. Measurements were performed before treatment and at 1, 3 and 6 months after treatment, respectively.

Statistical analysis

SPSS23.0 was used for statistical analysis. The measurement data were expressed as \( (\bar{x} \pm s) \) and compared by independent-samples t test. The counting data were expressed as \([n \%]\) and compared by \( \chi^2 \) test. Multipoint data were analyzed by ANVOA and compared by F test. The figures were plotted with Graphpad Prism 8. \( P < 0.05 \) was considered statistically significant.

Results

General data

No significant difference was found between the study and control groups in terms of gender, age, proportion of different types of CHDs and NYHA functional classification for heart failure at admission \( (P > 0.05) \), Table 1.

Captopril reduced serum BNP level

At 3 months after treatment, the serum BNP level in Group B was significantly higher than that before treatment, while the serum BNP level in Group A was significantly lower than that before treatment, and was significantly lower than that in Group B \( (P < 0.05) \). At 6 months after treatment, the serum BNP level in Group B was significantly higher than that before treatment and at 1 and 3 months after treatment, while the serum BNP level in Group A was lower than that before treatment and at 1 and 3 months after treatment, and was significantly lower than that in Group B \( (P < 0.05) \) (Figure 1).

Captopril reduced serum MMP-2 level

At 3 months after treatment, the serum MMP-2 level in Group B was significantly higher than that before treatment, while the serum MMP-2 level in Group A was significantly lower than that before treatment, and was significantly lower than that in Group B \( (P < 0.05) \). At 6 months after treatment, the serum MMP-2 level in Group B was significantly higher than that before treatment and at 1 and 3 months after treatment, while the serum MMP-2 level in Group A was significantly lower than that before treatment and at 1 and 3 months after treatment, and was significantly lower than that in Group B \( (P < 0.05) \) (Figure 1).

Captopril reduced serum TIMP-1 level

At 3 months after treatment, the serum TIMP-1 level in Group B was significantly lower than that before treatment, while the serum TIMP-1 level in Group A was significantly higher than that before treatment, and was significantly higher than that in Group B \( (P < 0.05) \). At 6 months after treatment, the serum TIMP-1 level in Group B was significantly lower than that before treatment and at 1 and 3 months after treatment, while the serum TIMP-1 level in Group A was significantly higher than that before treatment and at 1 and 3 months after treatment, and was significantly higher than that in Group B \( (P < 0.05) \) (Figure 2).

At 3 months after treatment, the serum MMP-9 level in Group B was significantly higher than that before treatment, while the serum MMP-9 level in Group A was significantly lower than...
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Table 1. Comparison of general data between the two groups (\(\bar{x} \pm s\)/[n (%)]

<table>
<thead>
<tr>
<th>General data</th>
<th>Group A (n = 44)</th>
<th>Group B (n = 43)</th>
<th>t/(X^2)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24 (54.55)</td>
<td>22 (51.16)</td>
<td>0.100</td>
<td>0.752</td>
</tr>
<tr>
<td>Female</td>
<td>20 (45.45)</td>
<td>21 (48.84)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.56±0.38</td>
<td>1.51±0.42</td>
<td>0.583</td>
<td>0.562</td>
</tr>
<tr>
<td>Type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple atrial septal defect</td>
<td>11 (25.00)</td>
<td>12 (27.91)</td>
<td>1.857</td>
<td>0.629</td>
</tr>
<tr>
<td>Simple ventricular septal defect</td>
<td>13 (29.55)</td>
<td>14 (32.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concurrent atrial septal defect and ventricular septal defect</td>
<td>8 (18.18)</td>
<td>7 (16.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>6 (13.64)</td>
<td>5 (11.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetralogy of fallot</td>
<td>2 (4.55)</td>
<td>1 (2.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>4 (9.09)</td>
<td>4 (9.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA functional classification for heart failure at admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>17 (38.64)</td>
<td>14 (32.56)</td>
<td>0.857</td>
<td>0.341</td>
</tr>
<tr>
<td>Class III</td>
<td>25 (56.82)</td>
<td>26 (60.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>2 (4.55)</td>
<td>3 (6.98)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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**Figure 1.** Comparison of BNP and MMP-2 levels between the two groups. BNP (A) and MMP-2 (B) levels before treatment and at 1 month after treatment in Group A showed no significant difference compared with those in Group B ($P > 0.05$), while the BNP and MMP-2 levels at 3 and 6 months after treatment in Group A were significantly lower than those in Group B ($P < 0.05$). * refers $P < 0.05$ for comparison between the two groups.

**Figure 2.** Comparison of TIMP-1 and MMP-9 levels between the two groups. TIMP-1 (A) and MMP-9 (B) levels before treatment and at 1 month after treatment in Group A showed no significant difference compared with those in Group B ($P > 0.05$), while the TIMP-1 and MMP-9 levels at 3 and 6 months after treatment in Group A were significantly higher than those in Group B ($P < 0.05$). * refers $P < 0.05$ for comparison between the two groups.

that before treatment, and was significantly lower than that in Group B ($P < 0.05$). At 6 months after treatment, the serum MMP-9 level in Group B was significantly higher than that before treatment and at 1 and 3 months after treatment, while the serum MMP-9 level in Group A was significantly lower than that before treatment and at 1 and 3 months after treatment, and was significantly lower than that in Group B ($P < 0.05$) (Figure 2).

**Captopril improved LVEF**

At 3 months after treatment, the LVEF in Group B was significantly lower than that before treatment, while the LVEF in Group A was significantly higher than that before treatment, and was significantly higher than that in Group B ($P < 0.05$). At 6 months after treatment, the LVEF in Group B was significantly lower than that before treatment and at 1 month after treatment,
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Figure 3. Comparison of LVEF level between the two groups. LVEF level before treatment (A) and at 1 month after treatment (B) in Group A showed no significant difference compared with those in Group B ($P > 0.05$), while the LVEF levels at 3 months (C) and 6 months (D) after treatment in Group A were significantly higher than those in Group B ($P < 0.05$). * refers $P < 0.05$ for comparison between the two groups.

while the LVEF in Group A was significantly higher than that before treatment and at 1 month after treatment, and was significantly lower than that in Group B ($P < 0.05$) (Figure 3).

Captopril reduced Tei index

At 3 months after treatment, the Tei index in Group A was significantly lower than that before treatment, while the Tei index in Group B was significantly higher than that before treatment, and was significantly higher than that in Group A ($P < 0.05$). At 6 months after treatment, the Tei index in Group B was significantly higher than that before treatment and at 1 month after treatment, while the Tei index in Group A was significantly lower than that before treatment and at 1 month after treatment, and was significantly lower than that in Group B ($P < 0.05$) (Figure 4).

Captopril reduced Qp/Qs

At 3 and 6 months after treatment, the Qp/Qs in Group A was significantly lower than that before treatment and at 1 month after treatment ($P < 0.05$), while the Qp/Qs in Group B was significantly higher than that before treatment and at 1 month after treatment ($P < 0.05$), and the Group A showed decreased Qp/Qs compared with Group B ($P < 0.05$) (Table 2).

Captopril reduced PASP

At 1, 3 and 6 months after treatment, the PASP in Group A was all significantly lower than that
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Table 3. Comparison of PASP level between the two groups before treatment and at different times after treatment (X ± s, mmHg)

<table>
<thead>
<tr>
<th>Grouping</th>
<th>Number of cases</th>
<th>Before treatment</th>
<th>1 month after treatment</th>
<th>3 months after treatment</th>
<th>6 months after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>44</td>
<td>32.16±1.42</td>
<td>30.48±1.48</td>
<td>29.31±1.62</td>
<td>26.83±1.57</td>
</tr>
<tr>
<td>Group B</td>
<td>43</td>
<td>32.34±1.58</td>
<td>33.75±1.43</td>
<td>34.58±1.58</td>
<td>35.61±1.84</td>
</tr>
<tr>
<td>t</td>
<td>0.559</td>
<td>10.477</td>
<td>15.357</td>
<td></td>
<td>23.962</td>
</tr>
<tr>
<td>P</td>
<td>0.578</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

before treatment (P < 0.05), while the PASP in Group B was all significantly higher than that before treatment (P < 0.05), and the PASP in Group A was all significantly lower than that in Group B (P < 0.05) (Table 3).

Discussion

The clinical concurrence of CHD complicated with pulmonary artery hypertension is relatively high. The blood flow in the pulmonary circuit associated with CHD involving a left-to-right shunt is significantly higher than that in patients with other shunt types, accompanied with pulmonary capillary vessels or pulmonary artery contraction, stenosis and even obstruction, which will cause progressive increase in pulmonary artery pressure and ultimately affect cardiac function [13]. The pathological mechanism of secondary pulmonary artery hyp-
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Hypertension in children with CHD has not been fully elucidated in clinic yet, but with the deepening of research, this understanding will be further developed [14, 15].

To explore the application value of angiotensin-converting enzyme inhibitor, we need to start from the renin-angiotensin system of the body, which exists in adrenal gland, kidney, circulatory system, heart and vascular wall as one of the body fluid regulation systems [16]. A study has found that angiotensinogen and renin genes are expressed in myocardium and vascular smooth muscle, which also contain a large amount of angiotensin II (Ang II) and angiotensin-converting enzyme (ACE), indicating that not only the systemic renin-angiotensin system but also some independent local renin-angiotensin systems exist in the body, and the latter is mainly found in cardiovascular tissues and may regulate cardiovascular activities through paracrine and autocrine secretion [17]. An experimental study has found that ACE II plays not only an important role in the renin-angiotensin system balance but also an important protective value in the occurrence and progression of pulmonary artery hypertension [18]. In this study, captopril, an angiotensin-converting enzyme inhibitor, was used for treatment in Group A. The results showed that within 6 months after treatment, MMP-2, MMP-9 and BNP decreased and TIMP-1 increased gradually in Group A, while Group B showed the opposite results, suggesting that if children with CHD were not treated with effective methods, the levels of MMP-2, MMP-9 and BNP would increase and TIMP-1 would decrease continuously. The levels of these indices could be effectively controlled through active treatment, indicating that captopril can control the pulmonary vascular remodeling in children with CHD to some extent. Captopril is an ACE inhibitor that inhibits angiotensin-converting enzyme activity. A study has found that pulmonary vascular remodeling is closely related to MMP-2 and MMP-9, and the control of MMP-2 and MMP-9 levels plays an important role in controlling pulmonary vascular remodeling [19]. Captopril effectively reduces BNP level by blocking the vasoconstriction of Ang II and reducing resistance in the systemic circuit, the work of cardiac systolic ejection and tension on cardiac muscle cells, thus reducing BNP secretion [20]. Connective tissue growth factor belongs to a class of fibrosis-promoting cytokine that can accelerate the generation of MMPs and extracellular matrix. The increase of MMPs level will accelerate the degradation of collagen components in extracellular matrix, and extracellular matrix will undergo remodeling, causing changes in the physiological characteristics of vascular wall, and finally leading to pulmonary vascular remodeling [21]. Captopril can tightly bind the active groups of MMPs by hydrogen bond and hydrophobic bond after administration and effectively inhibit the activity of MMPs, playing a cardiovascular protective role. Another study has also shown that angiotensin-converting enzyme inhibitors can be used as new MMPs inhibitors [22].

The LVEF index mainly reflects the left ventricular ejection efficiency, which should exceed 0.6 under normal conditions. The left ventricular function can be accurately determined by measuring the LVEF level [23]. In this study, LVEF increased, and Qp/Qs, Tei index and PASP decreased gradually within 6 months in Group A after administration of captopril, whereas the results in Group B were just the opposite, suggesting that active treatment is an important method to improve left ventricular function in children with CHD, which can improve cardio-pulmonary vascular dynamics in children and effectively prevent the development of pulmonary artery hypertension. The increase in LVEF by captopril is mainly due to the dilation of small vessels in the systemic circuit and the decrease of pressure in the systemic circuit after administration, so that the stroke volume increases accordingly and LVEF increases. Tei index is a new index with higher sensitivity and accuracy for evaluating the cardiac function of children with CHD, which is not affected by cardiac morphology, cardiac load and cardiac rate compared with commonly used cardiac function evaluation indices [24]. Under normal circumstances, Tei index is at a low level. Tei index will increase when the cardiac function decreases, and the lower the cardiac function is, the higher Tei index will be [25]. It has been shown that Tei index decreased gradually after treatment, which is because the application of captopril delays the deterioration of cardiac function in children with CHD. It has also been shown that after taking captopril, the systemic circuit of the children is relatively dilative, blood flow in systemic circuit is increased, and left-to-
right shunt volume is obviously reduced, Qp/Qs is therefore reduced. In addition, pulmonary artery pressure is correspondingly reduced following reduction of pulmonary circulation volume, so PASP was significantly reduced [26].

In conclusion, captopril treatment for children with CHD involving a left-to-right shunt can significantly improve the cardiac function, control the levels of serum indices and prevent the development of pulmonary artery hypertension. However, the study only included a small number of subjects with narrow age range. There is insufficient evidence on the correlation between pulmonary artery hypertension and CHD, so it is necessary to further study the deficiencies to provide more references for the treatment of CHD involving a left-to-right shunt in children.

Disclosure of conflict of interest

None.

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