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ORIGINAL ARTICLE

Effectiveness of Angiotensin-Converting Enzyme Inhibitors in Pediatric Patients with Mid to Severe Aortic Valve Regurgitation

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Abstract The long-term benefit of angiotensin-converting enzyme inhibitors in pediatric patients with aortic valve regurgitation is under consideration. Eighteen patients with mid to severe aortic valve regurgitation were retrospectively evaluated. Echocardiographic parameters (left ventricular end-diastolic diameter, shortening fraction, left ventricular posterior wall thickness, and grade of aortic valve regurgitation) were analyzed before and during therapy with angiotensin-converting enzyme inhibitors. Data are given as standard deviation scores (*Z*-scores) derived from body surface-adjusted normal values. Median (interquartile range) age at start of therapy was 8.4 (5.4 to 10.0) years, and total follow-up 2.3 (0.9 to 5.4) years. Left ventricular end-diastolic diameter increased from 3.6 (2.3 to 4.5) to 3.7 (2.4 to 4.8), and left ventricular posterior wall diameter decreased from 1.9 (1.1 to 3.0) to 1.1 (0.5 to 2.3). Grade of aortic valve regurgitation increased from 3.5 (2.3 to 4.0) to 4.0 (2.0 to 4.0), and shortening fraction decreased from 39% (34% to 43%) to 37% (34% to 42%). No significant effect of angiotensin-converting enzyme inhibitors on left ventricular dimensions or function was found in our population of patients with mid to severe aortic valve regurgitation. Angiotensin-converting enzyme inhibitors may not alter left ventricular overload in pediatric patients with aortic valve regurgitation.

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Introduction

Chronic aortic valve regurgitation is characterized by a diastolic backflow from the aorta into the left ventricle due to malcoaptation of the aortic valve cusps [19]. The regurgitant blood volume leads to a combined volume and pressure overload of the left ventricle [6]. To compensate this overload, the left ventricle dilates and hypertrophies and ends up in an eccentric left ventricular hypertrophy with the possible risk of left ventricular failure and death [2–4, 19].

Different options for the pharmacological treatment of aortic valve regurgitation such as diuretics, vasodilators, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors are available [1, 3, 11, 15–18, 20–22]. The reduction of volume load on the left ventricle by afterload reduction is the foremost desired effect. This may delay the progression of left ventricular dilatation, change of left ventricular geometry, and increase in myocardial mass [8, 14]. Angiotensin-converting enzyme inhibitors are frequently used in pediatric patients with congenital heart disease [1, 17–19]. Recent studies concerning the effect of angiotensin-converting enzyme inhibitor therapy in adults demonstrate controversial results [7, 11]. Pediatric studies addressing therapy of isolated aortic valve regurgitation are rare and limited.

Our objective was to evaluate the effect of angiotensin-converting enzyme inhibitors on ventricular dimensions and function in pediatric patients with mid to severe aortic valve regurgitation.

Materials and Methods

Patients

Between February 1988 and December 2005 all consecutive patients (age < 18 years) presenting with hemodynamically isolated mid to severe aortic valve regurgitation were included. Clinical charts and echocardiography data were analyzed retrospectively. Exclusion criteria were patients with combined aortic valve stenosis exceeding a mean gradient of 20 mm Hg, or peak gradient of 40 mm Hg, and patients with additional hemodynamically relevant cardiac defects such as ventricular septal defect or mitral valve disease. Further exclusion criteria were incomplete data and loss of follow-up.

Ethical approval for the study and data collection was obtained according to the guidelines of the local ethics committee.

Echocardiography

Echocardiographic analysis consisted of left ventricular end-diastolic diameter, left ventricular posterior wall thickness, shortening fraction, and aortic valve regurgitation measurements and were performed in short-axis or long-axis view in line with the recommendations of the American Society of Echocardiography [13]. The grade of aortic valve regurgitation was quantified by the area of regurgitant jet from the apical view in relation to the area of the left ventricular outflow tract (jet width ratio) and by the height of the regurgitant jet into the left ventricle from the parasternal long-axis view. Furthermore, pressure halftime, slope of decay, and reversal blood flow in descending thoracic aorta and abdominal aorta were measured. Classification of grading of the severity of aortic valve regurgitation was performed, based on recommendations of the American Society of Echocardiography [10, 23].

Drug Administration

Clinical criterion for treatment with angiotensin-converting enzyme inhibitors was a deterioration of left ventricular function, an increase in left ventricular dimensions beyond the 97th percentile, increasing grade of aortic valve regurgitation, or onset of symptoms such as dyspnea on exertion. As angiotensin-converting enzyme inhibitors, captopril was given at a dose of 1 mg/kg/day for infants and enalapril at a dose of 5–10 mg/m^2/day for children [5].

Data Analysis

Data are presented as median (interquartile range). To correct echocardiographic measurements for age and body surface area, standardized deviation scores (*Z*-scores) were calculated for normal values from Kampmann et al. [12]. Body surface area was calculated from height and weight as described by DuBois [9].

We analyzed the echocardiographic parameters before the start of angiotensin-converting enzyme inhibitor, at first clinical control under treatment, and at the end of follow-up.

Results

Our database revealed 24 patients with the diagnosis of mid to severe aortic valve regurgitation. Six patients were excluded due to incomplete data (n = 1), loss of follow-up (n = 2), or other reasons (n = 3). Finally, 18 patients were analyzed. Median (interquartile range) age at start of angiotensin-converting enzyme inhibitor therapy was 8.4 (5.4 to 10.0) years, and time of follow-up 2.3 (0.9 to 5.4) years. The cardiac diagnoses are reported in Table 1.

Time between start of angiotensin-converting enzyme inhibitor and first clinical control under treatment was 3.8 (2.4 to 6.9) months. Table 2 reports changes among start of angiotensin-converting enzyme inhibitor, first control under treatment, and last control. Left ventricular posterior wall diameter decreased under treatment. Left ventricular end-diastolic diameter decreased at first control under treatment but deteriorated until the end of follow-up. These changes were not statistically significant. The grade of aortic valve regurgitation deteriorated from 3.5 (2.3 to 4.0) to 4.0 (2.0 to 4.0). The analysis of each single patient shows that eight patients already had a grade of 4 at their first control, and seven of eight patients had no improvement under angiotensin-converting enzyme inhibitor therapy. Four patients increased from grade 2 resp. 3 to grade 3 resp. 4, whereas two patients showed no change

Table 1 Patient characteristics

Age at start of follow-up, yr (range)[a]	8.4 (5.4–10.0)
Time of follow-up, yr (range)[a]	2.3 (0.9–5.4)
Cardiac diagnosis	
CAVD	12
TAC	2
TGA	1
TOF	1
Postinfectious	2

Note. CAVD, congenital aortic valve disease; postinfectious, status after bacterial endocarditis or rheumatic fever; TAC, truncus arteriosus communis after surgical repair; TGA, transposition of the great arteries after arterial switch; TOF, tetralogy of Fallot after surgical repair

[a] Median (interquartile range)

Table 2 Comparison of echocardiographic parameters at start of follow-up, first control under treatment, and last control under treatment for patients with aortic valve regurgitation treated with ACE inhibitors

	Start of ACE	First control, treatment	Last control, treatment
LVEDD, *Z*-score	3.6 (2.3–4.5)	3.3 (2.8–4.0)	3.7 (2.4–4.8)
LVPWD, *Z*-score	1.9 (1.1–3.0)	1.5 (0.5–2.5)	1.1 (0.5–2.3)
AR grade	3.5 (2.0–4.0)	4.0 (2.0–4.0)	4.0 (2.0–4.0)
SF, %	39.0 (33.5–43.0)	39.5 (35.3–41.8)	36.5 (34.3–41.8)

Note. ACE, angiotensin-converting enzyme; LVEDD, left ventricular end-diastolic diameter; LVPWD, left ventricular posterior wall diameter; AR, aortic valve regurgitation; SF, shortening fraction; *Z*-score, standardized deviation score. Median (interquartile range)

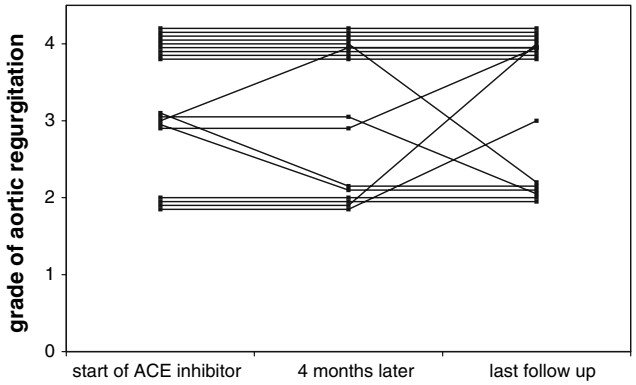

Fig. 1 Grade of aortic valve regurgitation at start of angiotensin-converting enzyme (ACE) inhibitor treatment; 4 months later, under treatment; and at last follow-up under treatment

and only four patients showed an improvement from grade 3 resp. 4 to a grade of 2 (Fig. 1).

Discussion

In our study angiotensin-converting enzyme inhibitor therapy in pediatric patients with mid to severe aortic valve regurgitation did not show any significant improvement of the left ventricular dilatation, left ventricular posterior wall thickness, shortening fraction, or grade of aortic regurgitation. Slight relief of the posterior wall thickness was evident due to reduction of the systemic afterload. The degree of aortic valve regurgitation was already mid to severe at the start of angiotensin-converting enzyme inhibitor therapy, but persisted as grade 4 aortic valve regurgitation in the majority of our patients. Therefore, the treatment with angiotensin-enzyme inhibitors showed no significant effect on the degree of aortic valve regurgitation. Left ventricular end-diastolic diameter showed an improvement at the first control after start of treatment, but increased progressively in the following clinical controls as reported in Table 2.

The first study concerning positive effects of angiotensin-converting enzyme inhibitors in adults with aortic valve regurgitation was published by Reske et al. [20]. In 1994, the positive effect of unloading therapy was confirmed by Lin et al. [15] and by Schon et al. [21]. The study by Lin et al. [15] compared enalapril with hydralazine. Both drugs showed a positive effect. Schon et al. [21] analyzed hemodynamic and morphologic changes after 1 year of angiotensin-converting enzyme inhibition with quinapril, although there was no control group.

The first study in pediatric patients concerning the positive effect of angiotensin-converting enzyme inhibitor therapy was carried out by Alehan et al. in 1998 [1]. Their study showed that in pediatric patients with chronic aortic regurgitation, long-term angiotensin-converting enzyme inhibitor therapy reduces regurgitant volume and favorably affects left ventricular volumes, dimensions, and hypertrophy. As study limitations they declared the absence of a control group and the rather short observation time of 1 year. However, most of their patients had aortic regurgitation due to rheumatic heart disease and the morphologic and functional changes may also be due to spontaneous myocardial recovery.

In 2000, Mori et al. [18] also reported positive effects during growth. However, they included patients with aortic valve regurgitation and patients with mitral valve regurgitation in their study. In contrast, the study in adults by Evangelista et al. [11]. was the first to report no difference in the clinical course of three groups. The first group was untreated, the second group was treated with nifedipine, and the third group was treated with enalapril. They analyzed probability of aortic valve replacement and left ventricular variables like diameter and ejection fraction in patients with asymptomatic, chronic, severe aortic valve regurgitation.

Numerous studies are available concerning afterload reduction with vasodilators or angiotensin-converting enzyme inhibitors in adults. The conflicting results may be due to methodical factors such as different patient characteristics, different drugs and dosages, or different hemodynamic and echocardiographic parameters.

Regarding the potential side effects and the costs of angiotensin-converting enzyme inhibitors, whether an application is justified must be carefully considered.

Study Limitations

The heterogeneous group of patients in terms of age and principal diagnosis, small patient number, progressed grade of aortic regurgitation, retrospective study design, and lack of invasive hemodynamic data are study limitations.

Conclusion

No effect of angiotensin-converting enzyme inhibitor therapy was shown in a small group of pediatric patients with mid to severe aortic valve regurgitation. There was only a possible effect on posterior wall diameter. In view of our results, the lack of long-term follow-up studies with large patient cohorts, and the controversial study results in adults, a prospective long-term multicenter follow-up study will be required, to increase the number of patients and to define a homogeneous study group of patients [16].

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