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Original Article

Profile of Pediatric Rheumatic Heart Disease Patients with Mitral Regurgitation Receiving Angiotensin-Converting Enzyme Inhibitor in dr. Saiful Anwar General Hospital Malang

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ABSTRACT

Background : ACE inhibitors through reverse remodeling mechanisms may encounter secondary LV changes due to rheumatic MR. Studies regarding RHD in Indonesia, however, remain limited.
Objectives : This study purposed to define the characteristic profile of pediatric rheumatic heart disease patients with mitral regurgitation who received ACE inhibitors.
Methods : This descriptive observational study involved 47 pediatric RHD patients in the Pediatric Cardiology Outpatient Department of dr. Saiful Anwar General Hospital from November 2018 to June 2019. Patients were divided into the captopril group and the no captopril group. The Captopril group was defined as patients who had been receiving captopril for more than or equal to 12 months prior to the study. Data about demographic and echocardiographic parameters were analyzed.
Results: Female patients were predominant (68%), with a mean age of 12.1 years and body mass index (BMI) of 17.2 kg/m2. The Captopril group revealed younger age, higher BMI, and longer initial time of RHD diagnosis compared to the no captopril group. Evaluation of LV remodeling parameters demonstrated that the captopril group had smaller LVIDd, lower LVMI, higher FS, and higher LVEF. LVPWd dan RWT were found to be relatively similar among both groups. Evaluation of MR grade revealed that the captopril group showed the lower value of MR VC, MR EROA, and MR regurgitant volume, as well.
Conclusion: Pediatric rheumatic MR receiving ACE inhibitors revealed smaller LVIDd, lower LVMI, lower MR grade, higher FS, and higher LVEF compared to patients receiving no ACE inhibitors.

1. Introduction

Rheumatic heart disease (RHD) is one of the most leading causes of morbidity and mortality of cardiovascular disease worldwide, especially in the pediatric population.[1] RHD occurs as a complication of acute rheumatic fever (ARF), in which 35% of patients diagnosed with ARF developed RHD after one year, and the rate increased to 51% after 10 years.[2] The incidence of ARF in children aged 5-14 years ranges from 300,000 – 350,000 per year, subsequently raises the incidence risk of RHD.[3]

Long-term consequences and sequelae of ARF may lead to further inflammation process contributing to valvulitis and carditis, and frequently causing isolated mitral regurgitation (MR - most common rheumatic valve abnormalities seen in children aged < 10 years), in which two-thirds of the population will develop mitral stenosis over more than 10 years due to extensive fibrosis and calcification.[4] Angiotensin-converting enzyme (ACE) inhibitor has been well-known for its reverse remodeling mechanism in degenerative MR. However, its study on rheumatic MR is still limited, particularly in Indonesia.[5] This study purposed to define the characteristic profile of pediatric rheumatic heart disease patients with mitral regurgitation who received ACE inhibitors.

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2. Method

2.1. Study design

This was a descriptive observational study with a collection of clinical and echocardiographic endpoints. Data were also obtained from outpatient medical records at Pediatric Cardiology Outpatient Department – dr. Saiful Anwar General Hospital, Malang, Indonesia from November 2018 to June 2019. A total of 69 patients were formerly enrolled. However, a total of 22 patients were excluded due to incomplete data or showing no mitral regurgitation on echocardiographic results. In brief, the inclusion criteria were aged < 18 years, diagnosed with RHD-MR, and has been receiving secondary prophylaxis Benzathine penicillin G injection within at least the past 12-months. Exclusion criteria were: 1) within the recurrent state of ARF; 2) congenital heart disease; 3) mitral stenosis; 4) no adherence to ACE inhibitor therapy; 5) history of infective endocarditis or having vegetation in mitral leaflet; 6) signs of congestion or dehydration; 7) history of valve replacement; 8) incomplete data on secondary prophylaxis; 9) parents' unwillingness to sign research informed consent. Patients then were divided into two groups: captopril (received captopril on a therapeutic dose of 0.3 – 0.5 mg/kg/dose t.i.d within past 12-months or more) and no captopril group. History taking regarding the compliance to ACE inhibitor was recorded via direct interview and monthly medication card. Baseline characteristics left ventricular remodeling parameters. Mitral valve regurgitation severity was variable measured in this study. Adherence was measured using a questionnaire (Morisky Medication Adherence Scale-8 [MMAS-8]). Adequate adherence was defined as MMAS-8 >6.[6]

2.2. Declaration

The study complied with the 1975 Declaration of Helsinki, and an Institutional Review Board or Local Ethical Committee approval was obtained in each participating subject. The aims, risks, and benefits of the study were explained to each participant, and they were asked to sign an informed consent form prior to enrollment. Participants were also informed that they could quit at any time during the interview session. Participation in this study was voluntary, and no incentive was given.

2.3. Outcomes

The grade of mitral regurgitation and left ventricular (LV) remodeling parameters were assessed using echocardiography. Echocardiography was performed by two cardiology residents under the supervision of a pediatric cardiologist who was experienced in RHD cases. Interobserver variability was calculated using Cohen's Kappa index of agreement, and we found the value of 0.82, indicating a perfect agreement among two residents.[7] We evaluated the grade of MR based on quantitative and semi-quantitative methods according to the recommendations of the European Association of Echocardiography for the Assessment of Valvular Regurgitation (2010), including MR Effective Regurgitant Orifice Area (EROA), MR Regurgitant Volume (MR RVol), and MR Vena Contracta (MR VC). We examine LV remodeling parameters including (1) LV dimension (left ventricular internal diameter in diastole [LVIDd], left ventricular posterior wall thickness at diastole [LVPWd], interventricular septal diameter [IVSd], fractional shortening [FS]); (2) LV mass and geometry (LV mass, left ventricular mass index [LVMI], relative wall thickness [RWT]); and (3) biventricular function, such as (left ventricular ejection fraction [LVEF], tricuspid annular plane systolic excursion [TAPSE], and LV diastolic function.[8]

2.4. Statistical analysis

Profile of distribution and proportion of study population were analyzed using descriptive statistics. Categorical variables were shown as frequency, cumulative frequency, and percentages. For continuous variables were expressed in mean and standard deviation (SD). All statistical analyses were performed with SPSS software Version 22.

3. Result

2.3. Baseline Characteristics

Our study population ranged from age 9 to 15 years, with a mean age of 12 years. There was predominantly female sex (68.1%) compared to male (31.9%) with a ratio of 2:1. The mean BMI of the sample was 17.2 kg/m2, mostly found with normal dietary status (57.4%). The majority of the study population was diagnosed and received secondary prophylaxis of benzathine penicillin-G within a mean time of 34 months. About 74.5% of the study population was receiving captopril in their monthly routine medication for at least 12 consecutive months.

The baseline echocardiographic parameters demonstrated that mean LVIDd was 4.25 cm, mean LVPWd 0.86 cm, and mean IVSd 0.69 cm. The mean fractional shortening was 61%. The mean LVMI of the samples was 95 gr/m2, with a mean RWT of 0.41. Right ventricular systolic function expressed a normal value with a mean TAPSE of 2.1 cm. The left ventricular systolic function of the study population was found normal, with a mean LVEF of 60%. Of the total population, LV diastolic dysfunction was expressed in 3 grades with the proportion of grade 1 (59.6%), grade 2 (27.6%), and grade 3 (12.8%), respectively. In LV geometry subcategories, the proportion of concentric remodeling was the highest (46.8%), followed by normal geometry, eccentric hypertrophy, and concentric hypertrophy (31.9%; 14.9%; 6.4%, respectively). Quantitative quantification of MR demonstrated that mean MR VC, MR EROA, and MR Reg Volume were 0.28 cm, 0.21 cm2, and 32 mL/beat, respectively. Qualitatively, mild MR was the most prevalent (83%), followed by moderate and severe MR (10.6% and 6.4%, respectively). Baseline and echocardiographic characteristics of the study population were shown in Table 1.

The sample population was furthermore classified into two groups, i.e., captopril and no captopril group. Female sex was seen to be predominant in both groups compared to male. The distribution of clinical and echocardiographic profiles among both groups was statistically analyzed to measure the dispersion and proportion without defining a cause-effect relationship (as shown in table 2). Captopril group demonstrated lower mean LVIDd (4.18 cm vs. 4.3 cm), higher mean IVSd (0.7 cm vs. 0.67 cm), higher mean LV fractional shortening (62% vs. 60%), lower mean LVMI (84 g/m2 and 88 g/m2, respectively), and higher mean LVEF (61% vs. 58%). Mean LVPWd, mean RWT and mean TAPSE among both groups were found to be similar (0.86 cm, 0.41, and 2.1 cm, respectively). The proportion of LV concentric remodeling was the highest in both groups compared to other LV geometry phenotypes (45.7% in captopril and 50% in no captopril group). LV normal geometry was the second-most prevalent LV geometry in both groups (31.4% in captopril and 33.3% in no captopril group). LV eccentric hypertrophy is the next common with the proportion of 14.3% in the captopril and 16.7% in the no captopril group. LV concentric hypertrophy was only expressed in the captopril group (8.6%). LV diastolic dysfunction grade 1 was the most prevalent in both groups (e.g., 57.1% in the captopril group and 66.7% in the no captopril group). Subsequently, LV diastolic dysfunction grade 2 was found in 25.7% of the captopril group and 33.3% of the no captopril group. LV diastolic dysfunction grade 3 was the least prevalent with the proportion of 17.2% only in the captopril group.

Mild mitral regurgitation was the most prevalent grade of MR in both groups (82.8% in captopril and 83.3% in no captopril group) qualitatively. Moderate MR was the second most, with the proportion of 8.6% in the captopril and 16.7% in the no captopril group, respectively. Severe MR was found in the captopril

group (8.6%) as compared to none in the no captopril group. This may explain through the mandatory use of captopril as anti-remodeling agents in patients with dilated LV with severe MR, as recommended by many current guidelines as well. Mild MR, in this case, may not be treated using captopril, based on the treating physician's preferences.

Mean quantitative MR measurements (e.g., MR VC, MR EROA, and MR Regurgitant Volume) were found to be lower in the captopril group compared to no captopril group (0.19 cm vs. 0.34 cm; 0.18 cm vs. 0.24 cm; 30 mL/beat vs. 32 mL/beat; respectively).

Table 1. Baseline characteristics of patients included in this study

Variable		Sample (n=47)
Baseline Characteristics		
Age (year) (mean ± SD)		12.12 ± 2.67
Sex	Male (n, %)	15 (31.9%)
	Female (n, %)	32 (68.1%)
Body Height (cm) (mean ± SD)		139 ± 12
Body Weight (kg) (mean ± SD)		34.7 ± 11.1
BMI (kg/m2) (mean ± SD)		17.2 ± 3.72
Time of RHD diagnosis (month) (mean ± SD)		33.8 ± 18.9
Dietary Status	Normal (n, %)	27 (57.4%)
	Skinny (n, %)	13 (27.6%)
	Obese (n, %)	7 (15%)
Captopril on	Yes (n, %)	35 (74.5%)
Daily Regimen	No (n, %)	12 (25.5%)
Echocardiographic Parameters		
LVIDd (cm) (mean ± SD)		4.25 ± 0.7
LVPWd (cm) (mean ± SD)		0.86 ± 0.12
IVSd (cm) (mean ± SD)		0.69 ± 0.13
LV Mass (gr) (mean ± SD)		99 ± 47
LVMI (gr/m2)(mean ± SD)		85 ± 22
RWT (mean ± SD)		0.41 ± 0.05
Left Ventricle Geometry	Normal (n, %)	15 (31.9%)
	Concentric Remodelling (n, %)	22 (46.8%)
	Concentric Hypertrophy (n, %)	3 (6.4%)
	Eccentric Hypertrophy (n, %)	7 (14.9%)
TAPSE (cm) (mean ± SD)		2.1 ± 0.4
LVEF (%) (mean ± SD)		60.5 ± 10.9
LV Diastolic Dysfunction		28 (59.6%)
	Grade 1 (n, %)	13 (27.6%)
	Grade 2 (n, %)	6 (12.8%)
Fractional Shortening (%)(mean ± SD)	Grade 3 (n, %)	61.3 ± 6.1
Quantitative MR Measurement	MR Vena Contracta (cm) (mean ± SD)	0.28 ± 0.19
	MR EROA (cm2) (mean ± SD)	0.21 ± 0.14
	RVol (mL/beat) (mean ± SD)	32 ± 11
Grade of MR	Mild (n, %)	39 (83%)
	Moderate (n, %)	5 (10.6%)
	Severe (n, %)	3 (6.4%)

Note, data were presented in mean ± SD or n(%); BMI = body mass index; EROA = effective regurgitant orifice area; IVSd = interventricular septal diameter; LV = left ventricular; LVIDd = left ventricular internal diameter in diastole; LVMI = left ventricular mass index; LVPWd = left ventricular posterior wall thickness at diastole; MR = mitral regurgitation; RHD = rheumatic heart disease; RVol = regurgitant volume; RWT = relative wall thickness; SD = standard deviation; TAPSE = tricuspid annular plane systolic excursion.

Table 2. Baseline characteristics of patients included in this study

Variable		Captopril (n=35)	No Captopril (n=12)
Baseline Characteristics			
Age (year) (mean ± SD)		12.01 ± 3.07	12.43 ± 1.49
Sex	Male (n, %)	10 (28.6%)	5 (41.7%)
	Female (n, %)	25 (71.4%)	7 (58.3%)
Body Height (cm) (mean ± SD)		138 ± 13	141 ± 7.0
Body Weight (kg) (mean ± SD)		34.6 ± 14.6	34.7 ± 7.2
BMI (kg/m2) (mean ± SD)		17.4 ± 4.46	16.8 ± 2.37
Time of RHD diagnosis (month) (mean ± SD)		34.4 ± 18.8	31.8 ± 19.1
Dietary Status	Normal (n, %)	20 (57.1%)	7 (58.3%)
	Skinny (n, %)	10 (28.6%)	3 (25%)
	Obese (n, %)	5 (14.3%)	2 (16.7%)
Echocardiographic Parameters			
LVIDd (cm) (mean ± SD)		4.18 ± 0.42	4.3 ± 0.56
LVPWd (cm) (mean ± SD)		0.86 ± 0.13	0.86 ± 0.12
IVSd (cm) (mean ± SD)		0.70 ± 0.14	0.67 ± 0.11
LV Mass (gr) (mean ± SD)		98.9 ± 29.8	99.1 ± 36.3
LVMI (gr/m2)(mean ± SD)		83.8 ± 18.9	88 ± 25.9
RWT (mean ± SD)		0.41 ± 0.05	0.41 ± 0.06
Left Ventricle Geometry	Normal (n, %)	11 (31.4%)	4 (33.3%)
	Concentric Remodelling (n, %)	16 (45.7%)	6 (50%)
	Concentric Hypertrophy (n, %)	3 (8.6%)	0 (0.0%)
	Eccentric Hypertrophy (n, %)	5 (14.3%)	2 (16.7%)
TAPSE (cm) (mean ± SD)		2.1 ± 0.4	2.1 ± 0.3
LVEF (%) (mean ± SD)		61.28 ± 10.2	58.3 ± 11.11
LV Diastolic Dysfunction	Grade 1 (n, %)	20 (57.1%)	8 (66.7%)
	Grade 2 (n, %)	9 (25.7%)	4 (33.3%)
	Grade 3 (n, %)	6 (17.2%)	0 (0.0%)
Fractional Shortening (%)(mean ± SD)		62.67 ± 3.65	60.8 ± 8.44
Quantitative MR Measurement	MR Vena Contracta (cm) (mean ± SD)	0.19 ± 0.17	0.34 ± 0.22
	MR EROA (cm2) (mean ± SD)	0.18 ± 0.10	0.24 ± 0.14
	R Vol (mL/beat) (mean ± SD)	30 ± 11	32 ± 12
Grade of Mitral Regurgitation	Mild (n, %)	29 (82.8%)	10 (83.3%)
	Moderate (n, %)	3 (8.6%)	2 (16.7%)
	Severe (n, %)	3 (8.6%)	0 (0.0%)

Note, data were presented in mean ± SD or n(%); BMI = body mass index; EROA = effective regurgitant orifice area; IVSd = interventricular septal diameter; LV = left ventricular; LVIDd = left ventricular internal diameter in diastole; LVMI = left ventricular mass index; LVPWd = left ventricular posterior wall thickness at diastole; MR = mitral regurgitation; RHD = rheumatic heart disease; RVol = regurgitant volume; RWT = relative wall thickness; SD = standard deviation; TAPSE = tricuspid annular plane systolic excursion.

4. Discussion

In this descriptive observational study, statistical analysis was used mainly to picture the profile of proportion, distribution, and behavior of the sample data using location (central tendency), dispersion, and shape statistics. This type of study has expressed no hypothesis and conclude no cause-effect relationship as a result. The presented data may be further utilized in the inferential or observational analytic type of research.

Baseline characteristics of the study population revealed that the sex proportion in RHD-MR patients was predominantly female (68.1%). This finding is consistent with the previous study by Lawrence et al. (2013) based on registries in Australia between 1997 – 2010, which showed that the proportion of female patients with RHD ranges from 65.8% to 71.1%. The mean age of our study was 12 years, and it was found to be similar with data from Northern Territory Australia that the highest ARF or RHD incidence occurred between 5-14 years with a mean age of 12 years.[3]

The mean BMI of our study population was 17.2% (with a range of 14 – 21 kg/m2), with normal dietary status. This finding is in line with a previous study by Beaton et al. (2012), which demonstrated that 64% of pediatrics aged 10-12 years with definitive RHD had normal BMI (16.5 kg/m2).[9]

Mean LVIDd was found to be lower in the captopril group compared to the no captopril group (4.18 cm and 4.3 cm, respectively), as well as in mean IVSd (0.67 cm vs. 0.7 cm). However, mean LVPWd was found similar among both groups. On the other hand, the mean fractional shortening in the captopril group was higher than the no captopril group (62.7% and 60.8%, respectively). Knirsch et al. (2010) reported significant improvement in LVIDd and LVPWd but not in IVSd and fractional shortening during 12-months follow-up of pediatric MR patients who received ACE inhibitor therapy.[10] Tunaoglu et al. (2004) also revealed an improvement in LV dilatation and fractional shortening in pediatric RHD-MR patients during 20-days treatment of ACE inhibitor.[11]

Either in captopril or in no captopril group has demonstrated LV concentric remodeling as the highest proportion of LV geometry phenotypes. Mean LVMI in the captopril group was found lower in the captopril group compared to the no captopril group (83,8 g/m2 and 88 g/m2, respectively). However, mean RWT among both groups demonstrated a similar measurement. Hence, this might be consistent with a previous study from Levine et al. (2006), which revealed 1-year treatment of ACE inhibitor in symptomatic RHD–MR patients significantly improved LV mass.[12]

Qualitative measurement of mitral regurgitation revealed that mild MR was the most prevalent in both groups. Quantitative measurement of mitral regurgitation using MR VC, MR EROA, and MR Regurgitant Volume was found to be lower in the captopril group, which supported the potential beneficial effect of captopril in improving MR severity. This finding was consistent with a previous study from Calabro et al. (1999). It was stated that treatment of ACE inhibitor in moderate-severe MR was associated with reduction of mitral valve regurgitation area (MR EROA), regurgitant volume, and regurgitant fraction.[13] However, whether the difference in the proportion of MR grade in our study population may possibly cause by reverse remodeling of LV (secondary MR) or due to the primary effect of ACE inhibitor towards valve repair (primary MR) still has to be further studied.

Both groups demonstrated good RV systolic function. LV diastolic dysfunction was found in all study populations, with the highest proportion of grade 1. Mean LVEF was found higher in the captopril group (61% vs. 58%, respectively). Corresponding to lower LVIDd and higher fractional shortening in the captopril group as mentioned above, higher LVEF, which has been shown, may be secondary to the improvement of LV dimension and MR severity simultaneously. This finding was parallel with a previous study from Tunaoglu et al. (2004).[11]

Our study has several limitations. First, this was a descriptive observational study. Thus cause-effect relationship may not be defined. Second, no complete data of previous transthoracic echocardiography as a comparison to our current echocardiographic result. Third, it included a relatively small number of patients thus could not represent the real picture of the entire population. Fourth, adherence or compliance was measured using MMAS-8, in which pill counting may emerge as a better alternative, particularly in vulnerable study populations.

5. Conclusion

Patients who received ACE inhibitors for more than or equal to 12 consecutive months revealed lower LVIDd, smaller LVMI, higher IVSd, greater LVEF, and higher fractional shortening. Moreover, patients who received ACE inhibitors demonstrated lower MR VC, MR EROA, MR regurgitant volume; compared to patients who did not receive ACE inhibitors.

6. Declarations

6.1. Ethics Approval and Consent to participate
This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involve in the study.

6.2. Consent for publication
Not applicable.

6.3. Availability of data and materials
Data used in our study were presented in the main text.

6.4. Competing interests
Not applicable.

6.5. Funding source
Not applicable.

6.6. Authors contributions
Idea/concept: FAS. Design: FAS. MSR. Control/supervision: MSR, AR, HM, IP. Data collection/processing: FAS, TRM. Extraction/Analysis/interpretation: FAS, TRM. Literature review: MSR, AR, HM, IP. Writing the article: FAS, MSR. Critical review: MSR, AR, HM, IP. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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