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Echocardiographic Parameters Correlated with Age in Isolated Severe Rheumatic Mitral Stenosis Patients in Indonesia

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Abstract

BACKGROUND: Despite the high prevalence of rheumatic mitral stenosis (MS) in Indonesia, the impact of aging on the anatomical and hemodynamic component of rheumatic MS is not well studied.

AIM: To analyze the association of age with various echocardiographic parameters in patients with isolated severe rheumatic MS in Indonesia.

METHODS: A cross-sectional study was conducted enrolling 263 subjects with isolated severe rheumatic MS who underwent transthoracic echocardiography (TTE) during January 2015 until December 2017 at National Cardiovascular Center of Harapan Kita, Jakarta, Indonesia. Demographic data were collected, and echocardiographic variables were measured based on standard TTE examination using GE Vivid 7 and S6 Doppler Echocardiography System (GE Medical System, Norway).

RESULTS: Of 263 subjects, there are 84 men and 179 women aged 18-80 (mean age 42.9) years old. Most patients had atrial fibrillation (80%), with a higher prevalence of AF in the older group. Age was positively correlated with LA diameter and Wilkin's score ($r = 0.186$, $P = 0.002$; $r = 0.142$, $P = 0.022$; respectively); while mean MVG ($r = -0.304$, $P < 0.001$), TR Vmax ($r = -0.126$, $P = 0.04$), TR maxPG ($r = -0.127$, $P = 0.039$) and TAPSE ($r = -0.125$, $P = 0.044$) were correlated negatively with age. Mean MVG has the strongest correlation with age in our subjects.

CONCLUSION: This is the first study in Indonesia that analyze the association of age and different echocardiographic parameters in isolated severe rheumatic severe MS patients. Age has a significant correlation with mean MVG, LA diameter, Wilkin's score, TR Vmax, TR maxPG, and TAPSE. We assume that the association of age and these parameters were influenced by the normal aging process and progression of chronic MS.

Introduction

Mitral stenosis (MS) is characterized by a decrease in mitral valve (MV) orifice area, causing blood flow obstruction from left atrium to left ventricle. The consequence is stagnation of blood proximal to the MV that results in the elevated pressure of left atrium, pulmonary venous, pulmonary artery, and right heart [1], [2]. Mitral stenosis is most commonly caused by rheumatic heart disease (RHD) with typical rheumatic features such as commissural fusion, leaflet thickening and calcification that primarily affects the leaflet tips, and chordal fusion and shortening [3]. Mitral stenosis is highly prevalent in developing countries because of its association with the prevalence of rheumatic fever, although degenerative MS is now more prevalent in the developed countries [4], [5]. The incidence and prevalence of RHD vary greatly among different age groups and regions of the world. The global prevalence of RHD is around 1 per 1,000 in children aged 5-14 years. There is no current data on the prevalence of rheumatic MS in Indonesia, but based on the study by Carapetis *et al.*, Indonesia was included in the Asia region (East and Southeast Asia, excluding China and Japan) which had a prevalence of 0.8 per 1,000 [4].

The diagnosis of rheumatic MS is made

based on clinical examination and echocardiography findings. However, most symptoms occur at the later stage of the disease, which usually leads to late diagnosis and increased morbidity and mortality. Most RHD cases we face in the clinics in Indonesia are greater than moderate in severity due to low health literacy of the low-income population. Echocardiography has been used widely to confirm the diagnosis, determine the aetiology of MS and its severity, and evaluation of other valve lesions. It can also provide more detailed information which helps to decide for the management, whether it is percutaneous or surgical intervention [6].

Rheumatic MS is more common in female and typically presents in the third or fourth decade of life while degenerative MS in the seventh and eighth decades [7]. Aging itself leads to significant cardiovascular structural changes, which may impact the pathologic process of rheumatic MS. Despite the high prevalence of rheumatic MS in Indonesia, the impact of age and ageing process on the anatomical and hemodynamic component of rheumatic MS is not well studied.

Our study mainly focused on echocardiographic data (anatomical, hemodynamic and heart function) of isolated severe rheumatic MS cases in National Cardiovascular Center Harapan Kita, Jakarta, Indonesia, and the correlation of age with various echocardiographic parameters.

Methods

We conducted a cross-sectional study using data from the echocardiography registry of valvular heart disease at Harapan Kita National Cardiovascular Center, Jakarta, Indonesia. Total of 263 patients with a confirmed diagnosis of isolated severe rheumatic MS that underwent transthoracic echocardiography examination from January 2015 to December 2017 was included in the present study. Diagnosis of rheumatic MS was confirmed based on WHO criteria and 2014 AHA/ACC Valvular Heart Disease Guideline [8], [9]. Severe MS is defined by a mitral valve area ≤ 1.0 cm^2 either by planimetry or PHT method [2]. In this study, we only included severe isolated rheumatic MS patients without significant mitral regurgitation and aortic lesions. Patients with more than mild mitral regurgitation (MR) and / or aortic valve disease and history of previous percutaneous commissurotomy or surgical valve repair or replacement were excluded from this study.

Demographic data recorded was age, sex, body weight and height, body surface area (BSA) and blood pressure. Patients were classified as in sinus rhythm (SR) or atrial fibrillation (AF) based on their baseline electrocardiogram. For display purpose, several data were presented in two age categories, < 50 and ≥ 50 years old. This categorization was to show the value difference between younger and older subjects' group, cutoff age of 50 years old was chosen based on previous studies on aging and cardiovascular structural and functional changes [10].

Transthoracic echocardiography (TTE) examination was carried out in all cases using GE Vivid 7 and S6 Doppler Echocardiography system (GE Medical System, Norway). Echocardiographic examination was performed by experienced sonographers and calculated by two cardiologists. All echocardiographic parameters, including mitral valve area (MVA) by 2D planimetry and pressure half time (PHT) method, mean transmitral valve gradient (mean MVG), left atrial (LA) diameter, LA volume index (LAVI), left ventricular ejection fraction (LVEF), LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), tricuspid annular plane systolic excursion (TAPSE), tricuspid regurgitation (TR) severity, TR maximal velocity (TR Vmax), tricuspid valve maximum gradient (TR maxP), pulmonary valve acceleration time (PV AccT), right ventricular outflow tract velocity time integral (RVOT VTI), Wilkin's score, presence of spontaneous echo contrast (SEC) and thrombus at LA were assessed based on recommendations from the latest American Society of Echocardiography guidelines [11], [12], [13].

Baseline data, including echocardiographic values, were expressed descriptively, and the correlations between age and all echocardiographic parameters were analysed by Pearson's correlation test. In all statistical analyses, $P < 0.05$ indicated a significant correlation between means.

Results

This study enrolled 263 patients, 84 men and 179 women, with an age range of 18-80 (mean age 42.9) years old. Seventy-five percent of the subjects aged under 50 years old. Most patients had atrial fibrillation (80%), but less than half of them (43%) had SEC at LA, and even only 42 patients (16%) appeared to have thrombus at LA when examined with TTE. Compared to the younger patients, older patients (> 50 years old) had a higher percentage of AF (96.9% *vs* 75.1%). The severity of TR varies with mild TR is the most common (43.3%) followed by moderate and severe TR (29.3% and 20.9%, respectively). All patients had severe MS based on both MVA planimetry and PHT values that ranged between 0.3-1.0 cm^2, with mean MVG as low as 1.7 mmHg and highest of 25 mmHg (mean 12.18 mmHg). Interestingly, 71 patients (27%) had mean MVG lower than 10 mmHg, with a bigger percentage at subjects aged ≥ 50 years old compared to < 50 years old (43.9% vs 21.3%). Baseline characteristics and

echocardiographic values are shown in Table 1.

Table 1: Baseline characteristics and echocardiographic values

Baseline characteristics (Total N = 263)	N (%) or Mean±SD
Age (years), mean ± SD	42.94 ± 10.05
Age (years)	
< 50	197 (75%)
≥ 50	66 (25%)
Gender	
Female	179 (68%)
Male	84 (32%)
Body height (cm)	157.6 ± 7.95
Body weight (kg)	53.2 ± 12.09
Atrial fibrillation	208 (80%)
LASEC	116 (44.1%)
LA Thrombus	42 (16.1%)
TR severity	
Trace	17 (6.5%)
Mild	114 (43.3%)
Moderate	77 (29.3%)
Severe	55 (20.9%)
Echocardiographic parameters	
Mean MVG (mmHg)	12.18 ± 4.08
MVA PHT (cm^2)	0.69 ± 0.18
MVA Planimetry (cm^2)	0.74 ± 0.24
Wilkin's score	7.90 ± 1.47
LAVI (ml/m^2)	126.26 ± 85.28
LA diameter (cm)	5.34 ± 0.89
LV EF (%)	60.02 ± 10.03
LV EDD (cm)	4.28 ± 0.68
LV ESD (cm)	2.93 ± 0.59
TAPSE (cm)	1.7 ± 0.48
TR Vmax (m/s)	3.63 ± 0.77
TR maxPG (mmHg)	55.28 ± 22.69
PV AccT (ms)	88.07 ± 22.15
RVOT VTI (cm)	11.19 ± 3.81

Abbreviations: LASEC, left atrial spontaneous echo contrast; LA, left atrium; TR, tricuspid regurgitation; MVG, transmitral valve gradient; MVA, mitral valve area; PHT, pressure half time; LAVI, left atrial volume index; LV, left ventricular; EF, ejection fraction; TAPSE, tricuspid annular plane systolic excursion; Vmax, maximal velocity; maxPG, maximum pressure gradient; PV AccT, pulmonic valve acceleration time; RVOT VTI, right ventricular outflow tract velocity time integral; EDD, end-diastolic diameter; ESD, end-systolic diameter.

The correlation test showed that age was positively correlated with LA diameter and Wilkin's score (r = 0.186, *P* = 0.002; r = 0.142, *P* = 0.022; respectively), while negatively correlated with mean MVG (r = -0.304, *P* < 0.001), TR Vmax (r = -0.126, *P* = 0.04), TR maxPG (r = -0.127, *P* = 0.039) and TAPSE (r = -0.125, *P* = 0.044) (Table 2).

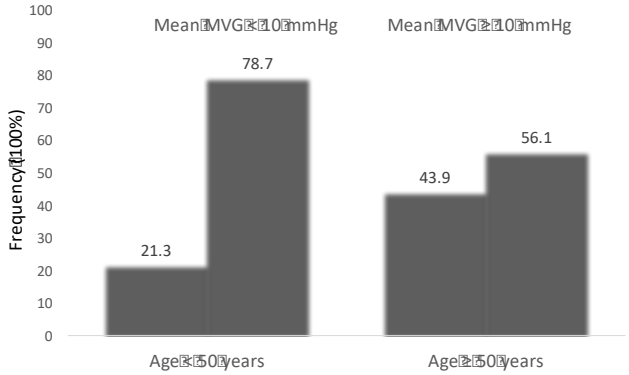

Figure 1: Frequency of subjects with means MVG < 10 mmHg and ≥ 10 mmHg in younger (< 50 years old) and older age (≥ 50 years old) groups

Among these parameters, mean MVG has the strongest correlation with age in our subjects. Majority of the younger subjects (< 50 years old) had higher mean MVG, 155 (78.7%) subjects with mean MVG ≥ 10 mmHg compared to 42 (21.3%) subjects with mean MVG < 10 mmHg. Meanwhile, this proportion shifted among older subjects (≥ 50 years old). The percentage of older patients with lower MVG was higher than the younger subjects, where 29 (43.9%) subjects with mean MVG < 10 mmHg and 37 (56.1%) subjects with mean MVG ≥ 10 mmHg (Figure 1).

Table 2: Correlation of age and various echocardiographic parameters

Parameters	Age (years)	
	r	*P*
Mean MVG (mmHg)	-0.314	<0.001*
MVA PHT (cm^2)	0.093	0.131
MVA Planimetry (cm^2)	0.012	0.853
Wilkin's score	0.142	0.022*
LAVI (ml/m^2)	0.098	0.113
LA diameter (cm)	0.186	0.002*
LV EF (%)	-0.017	0.779
LV EDD (cm)	-0.030	0.623
LV ESD (cm)	-0.008	0.900
TAPSE (cm)	-0.125	0.044*
TR Vmax (m/s)	-0.126	0.041*
TR maxPG (mmHg)	-0.127	0.039*
PV AccT (ms)	-0.046	0.462
RVOT VTI (cm)	0.061	0.333

*Statistically significant.

Discussion

In our study, there were more patients under the age of fifty years, with a percentage of 75% of the total sample. This is in accordance with the results of other studies which showed the highest prevalence of rheumatic MS is in adults aged 20–50 years [4], [14]. Both rheumatic MS and mitral annular calcification have been described in previous studies to be more common in women, two to four times more prevalent in women than men, whereas mitral regurgitation has similar prevalence between men and women [14], [15], [16]. Our study showed a marked female predominance in isolated rheumatic MS with a two-fold higher incidence in women than men. The scientific reasons for this female predominance had not been well explained, but some studies had proposed that it might be associated with social factors such as childbearing, which might increase exposure to group A streptococcus, access to health care, and genetic factors that predispose women to autoimmune diseases [14].

Mitral stenosis is associated with increased LA stiffness, LA remodelling, and abnormal contractility. In the setting of MS, LA enlargement due to pressure overload is usually secondary to increased LA afterload. This causes LA compliance reduction, increased LA and pulmonary pressures and right heart failure [17]. The impact of ageing on LA size had been established at the study by Nikitin *et al.*, LA diameter was increased with age with significantly higher LA diameter in the oldest subjects [18]. This supports our study finding that LA diameter had a significant positive correlation with age in our study, which means that the older the patient, the bigger or more dilated the LA.

Epidemiological studies had shown that generally, the prevalence and incidence of AF increased steeply after 65 years of age [19]. Atrial fibrillation and LA thrombus frequently complicate rheumatic mitral valve disease with 30-40% of patients had AF in long-term follow-up. The occurrence of AF correlates well with LA size; the incidence of AF increases from 3% when LA diameter is < 40mm to 54% if LA diameter is > 40 mm [20]. A study by Kim *et al.,* showed that the annual AF development rate was 3.5% in rheumatic MS patients with sinus rhythm that increased with LA size and MS severity. Meanwhile, MS patients with enlarged LA had an average AF development rate of 6.0% per year [21]. In rheumatic MS, enlarged LA combined with older age leads to very high AF prevalence as shown by our subjects. Eighty-percent of our subjects had AF, which is an even bigger percentage compared to previous studies. Almost all of older patients in our study had AF (96.9%). González-Torrecilla *et al.* found that the prevalence of SEC and thrombus at LA observed by TTE and transesophageal echocardiography (TEE) in MS patients with chronic AF is 52% and 29.5% [22]. In this study, the prevalence of SEC and thrombus is 43% and 16%. This lower prevalence in our study might be due to our method that only included results from TTE since thrombus at LA and LA appendage is easier to observe during TEE study.

Currently, there are no studies on the impact of age on the size of MVA by any measurement methods. MVA is one criterion to determine the anatomical severity of rheumatic MS, and in our study, we only included severe rheumatic MS patients (MVA ≤ 1.0 cm^2). Our study showed no correlation between age and both MVA planimetry and MVA PHT. We assumed that the degree of the valve stenosis is rather fixed throughout life and not being progressive over the years. Interestingly, Wilkin's score, that defines mitral valve score by calculating the individual subcomponent scores, including leaflet thickening and mobility, valve calcification, and subvalvular disease, is significantly correlated with age in our study. Ramakrishna and Kanattu had shown that despite the similarity in MVA between younger and older subjects, total mitral valve score < 8 was more common in the younger group with score > 11 was statistically more common in the older group. Older patients had higher leaflet calcification and subvalvular thickening score (> 2) compared to younger patients [23]. Older patients tend to have higher degenerative changes, although these changes might not have an impact on the degree of the mitral stenosis severity. Thus, older patients might not be suitable for percutaneous commissurotomy due to higher Wilkin's score. For cardiologists, this data will help decide the management of older rheumatic MS patients.

Mean MVG or the transmitral pressure gradient represents hemodynamic severity rather than anatomic severity and more closely associated with the patient's hemodynamic status. Mean MVG had the strongest significant correlation with age in our study (r = -0.314, *P* < 0.001). It is inversely correlated with age. Thus older patients had lower mean MVG. A recent study that supports our finding is by El Sabbagh *et al.,* which showed patients with low gradient severe MS (mean MVG < 10 mmHg) were older when compared to high gradient MS (mean age 65 ± 10 vs 56 ± 13 years old, *P* < 0.001) [24]. Although it had not been studied before, lower mean MVG in older patients might be due to several cardiovascular changes that happen with the normal aging process, including increased LV end-diastolic pressure, decreased LA compliance, higher heart rate and lower cardiac output [10]. Mitral stenosis itself increases LA pressure that leads to a reduction of LA compliance [17]. As chronic rheumatic MS patients get older, these factors will gradually lead to hemodynamic changes that cause lower mean MVG. Other factors that influence mean MVG are MVA, heart rate, cardiac output, LV and LA compliance, and other associated valve lesions. We excluded other significant mitral and aortic valve diseases, and our patients had similar MVA regardless of the age difference. Therefore, the mean MVG was not influenced by these factors in our study.

In patients with severe MS, persistently raised LA pressure results in pulmonary venous hypertension, reflex pulmonary arteriolar constriction, obliterative changes in the pulmonary vascular bed, pulmonary artery hypertension (PAH), RV hypertrophy and dilatation and tricuspid valve dysfunction [25]. Peak TR velocity (TR Vmax) is used to measure the pressure difference between the right atrium (RA) and RV using simplified Bernoulli equation (P = 4 $[TRmax]^2$) [26]. This method correlates well with PASP on right heart catheterisation [27]. Elevated TR Vmax (≥ 2.8 m/s) is highly accurate in correctly identifying pulmonary hypertension [28]. Our findings showed high TR Vmax and TR maxPG with low PV AccT and RVOT VTI, which all support the signs of pulmonary hypertension in rheumatic severe MS patients. Both TR Vmax and TR maxPG had a significant negative correlation with age (r = -0.126, *P* = 0.04; r = -0.127, *P* = 0.039; respectively). Several studies showed that pulmonary hypertension is greater in younger patients. Sinha *et al.* found that mean pulmonary arterial pressure and pulmonary vascular resistance are greater in juvenile MS patients compared to adults [29]. Studies by Tandon *et al.* and Ramakrishna and Kanattu showed that more severe pulmonary vascular changes and significant pulmonary hypertension were more common in younger patients [23], [30]. Lower TR Vmax and TR maxPG in elderly might also caused by greater RA and RV dilation which creates equalisation of RA and RV pressures, leading to underestimation of PA pressure by echocardiography.

Age is also correlated negatively with TAPSE in our study. TAPSE, which represents RV systolic

function, decreases with age [31]. RV hypertrophy and dilation due to chronic MS also leads to reduced RV function [25]. This pathophysiological changes in older rheumatic MS patients explain the mechanism of reduced TAPSE in this study.

In conclusion, this study is the first one that analyzes the correlation of age and different echocardiographic parameters in isolated severe rheumatic MS patients. Mean MVG had the strongest significant correlation with age in our study. Age had a significant positive correlation with LA diameter and Wilkin's score, while mean MVG, TR Vmax, TR maxPG, and TAPSE were found to be negatively correlated with age. The impact of the aging process on cardiovascular changes combined with a progression of chronic MS as the patient gets older leads to the association of those echocardiographic parameters with age. Our study results will help cardiologists, especially in a developing country who deal with more rheumatic MS patients, to understand more on the impact of ageing on the progression of rheumatic MS.

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