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Does Chronic Inflammation Play a Role in Rheumatic Mitral Valve Restenosis After Percutaneous Transvenous Mitral Commissurotomy?

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Abstract

Background: Mitral valve restenosis is defined as decreased mitral valve area (MVA) <1.5 cm2 or decreased MVA >50% after PTMC. It is time-dependent and associated with major adverse cardiovascular events (MACE), such as congestive heart failure, cardiac death, mitral valve replacement, and redo PTMC. The mechanism is not yet known; however, chronic inflammation may have a role.

Objective: To know the association between chronic inflammation and mitral valve restenosis after PTMC.

Methods: A total of 40 patients with mitral valve stenosis who underwent successful PTMC were matched and classified into restenosis/case group (n=20) and no restenosis/control group (n=20). Secondary data was taken from electronic medical records such as patient characteristics (gender, age & 2nd prophylaxis), echocardiography data before PTMC (Wilkins' score and MVA before PTMC), and echocardiography data after PTMC (MVA after PTMC). Follow-up echocardiography examination (follow-up MVA) and laboratory assessment of chronic inflammation marker (IL-6) were done on all patients. Statistical analyses were done to look for an association between the level of chronic inflammation marker & other independent variables with mitral valve restenosis.

Results: Median IL-6 concentration was 2.39 (0.03 – 11.4) pg/mL. There was no statistically significant difference in IL-6 levels between both groups (p-value >0.05). MVA decrement was 0.13 (0 – 0.62) cm2/year with rate of MVA decrement ≥0.155 cm2/year was predictor of mitral valve restenosis (p-value <0.001, OR = 46.72, 95% CI 6.69 – 326.19).

Conclusion: Chronic inflammation assessed by IL-6 was not associated with mitral valve restenosis.

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Keywords: Mitral valve restenosis, PTMC, chronic inflammation.

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Introduction

Rheumatic heart disease (RHD) is a global health problem often found in developing countries, including Indonesia.[1] RHD is characterized by long-term damage to the heart valves due to single or repeated episodes of acute rheumatic fever (ARF) caused by *Group A β-hemolytic Streptococcus* (GAS) infection. The pathogenesis of RHD is an autoimmune response mediated by humoral and cellular immunity leading to a chronic inflammatory process mediated by T lymphocytes, especially Th1 and Th17.[2,3]

Mitral valve stenosis is the most common heart valve abnormality found in RHD patients. Structural valve abnormalities are commissure fusion, chordal fusion and shortening, leaflet thickening and retraction, and leaflet calcification.[4] Percutaneous transvenous mitral commissurotomy (PMTC) is a non-surgical invasive treatment using balloon inflation usually done in patients with moderate-to-severe mitral valve stenosis. After the procedure, patients generally show clinical improvement due to an increase in the mitral valve area (MVA) and a decrease in the mitral valve gradient (MVG). However, during the follow-up period, mitral valve restenosis often occurs. Mitral valve restenosis is defined as decreased mitral valve area (MVA) <1.5 cm^2 or decreased MVA >50% after PTMC.[5] It is time-dependent and associated with major adverse cardiovascular events (MACE), such as congestive heart failure, cardiac death, mitral valve replacement, and redo PTMC. The mechanism is not yet known; however, chronic inflammation may have a role.[6] Several observational studies conducted on RHD patients who underwent PTMC showed high levels of pro-inflammatory cytokines such as IL-6, IL-8, and TNF β.[7,8] *Rifaie et al*. stated that chronic inflammation plays a role in mitral valve restenosis. There is an increase in IL-6 levels in patients with mitral valve restenosis.[7] IL-6 plays a role in B cell maturation and accelerates autoantibodies production. In addition, IL-6 and TGF-β play a role in producing other proinflammatory cytokines, IL-17.[9] Inflammation, either due to pathological injury or abnormal hemodynamic/mechanical stress, causes valvular interstitial cell activation and differentiation leading to further valvular damage due to fibrosis and calcification.[10]

Methods

Study Population

The study was performed in January – December 2021 at National Cardiovascular Centre Harapan Kita (NCCHK), Jakarta, Indonesia. A total of 40 patients with mitral valve stenosis who underwent successful PTMC from January 2016 – December 2019 were matched and classified into restenosis/case group (n=20) and no restenosis/control group (n=20). The criterion of successful PTMC was MVA after PTMC >1.5 cm2 or an increase of 50% of MVA without moderate-severe mitral valve regurgitation. Exclusion criteria were 1) Echocardiographic data were incomplete, 2) Patient had undergone mitral valve replacement surgery, 3) History of acute or chronic inflammatory/infectious diseases, 4) History of malignancy, and 5) Impaired renal function (eGFR <60 ml/min/1.73 m^2). Informed consent was taken from all subjects, and ethical clearance was granted by the Ethics Committee of National Cardiovascular Centre Harapan Kita (NCCHK), Jakarta, Indonesia.

Echocardiography Examination

Baseline MVA (MVA after PTMC) was taken from echocardiography data from the electronic medical record. It is calculated using MVA planimetry (2D). Follow-up MVA was calculated using MVA planimetry (2D). Mitral valve restenosis is defined as decreased MVA <1.5 cm^2 or decreased MVA >50% after PTMC. Follow-up duration was calculated from the date of PTMC until the follow-up echocardiography examination was done. Subjects were classified into restenosis/case group if MVA follow-up is <1.5 cm^2 or decreased >50% from baseline, and no restenosis/control group if not fulfilling mitral valve restenosis criteria. The rate of MVA decrement (in cm2/year) was calculated from the difference between MVA after PTMC and follow-up MVA divided by the duration of follow-up for each patient.

Laboratory Examination

IL-6 was measured in plasma samples using a commercially available capture ELISA Kit (D6050 R&D System Human IL-6 Quantikine ELISA Kit). IL-6 was measured once during follow-up period regarding its role in chronic inflammation on mitral valve restenosis.[7]

Statistical Analysis

Gender was classified into male group and female group.[3,11] MVA after PTMC was classified into ≤1.8 cm^2 and >1.8 cm^2.[6,12] Wilkins' score was classified into ≥8 and <8.[12,13] Secondary prophylaxis compliance was classified into poor and good compliance based on study criteria. Poor compliance was defined if the patient had not received >2 injections in the last 12 months or not consumed >24 hours of oral drugs in the last 30 days.

The Statistical Package for Social Science (SPSS, Chicago, IL, USA) program, version 26.0, was used for data analysis. Categorical data were presented in frequency and proportion. Numerical data were presented as mean ± SD if normally distributed or median (minimum-maximum) if not normally distributed. To analyze the relationship between inflammatory markers (IL-6) levels with mitral valve restenosis, the unpaired t-test or the Mann-Whitney test was performed. To explore the relationship of confounding variables (gender, MVA after PTMC & rate of MVA decrement, Wilkins' score, and compliance of secondary prophylaxis) with mitral valve restenosis, a Chi-square test or Fischer test was performed. The multivariate analysis was done using logistic regression for dependent variables with a p-value <0.25 in bivariate analysis. The odds ratio (OR) and confidence interval (CI) were calculated. Statistical test results are considered significant if the p-value <0.05.

Results

This case-control study included 11 male (27.5%) and 29 female (72.5%) patients; their ages ranged from 26 – 64 years old (mean 45.99 ± 10.11 years old). The median follow-up duration was 2.21 (0.74 – 7.83) years. The mean MVA after PTMC was 1.76 ± 0.28 cm^2 in the restenosis group and 1.92 ± 0.24 cm^2 in the no restenosis group. The mean rate of MVA decrement was 0.28 ± 0.14 cm^2/year in the restenosis group and 0.02 (0 – 0.18) cm^2/year in the no restenosis group. The median IL-6 level was 2.39 (0.03 - 11.4) pg/mL **(Table 1)**.

The rate of MVA decrement was classified into ≥0.155 cm^2/year and <0.155 cm^2/year based on ROC curve analysis which AUC of 0.970 was obtained for a rate of MVA decrement of 0.155 cm^2/year with a

Table 1. Clinical, echocardiography, and laboratory baseline characteristics of the studied group.

Variables	Total (n = 40)	Restenosis (n = 20)	No Restenosis (n = 20)	P value
Age (year)	45.99 ± 10.11	44.40 ± 10.99	47.59 ± 9.13	0.325
Age ≥50 years old (n, %)	15 (37.5%)	7 (35%)	8 (40%)	0.744
Gender, Female (n, %)	29 (72.5%)	15 (75%)	14 (70%)	0.723
MVA after PTMC (cm^2)	1.84 ± 0.27	1.76 ± 0.28	1.92 ± 0.24	0.054
MVA follow-up (cm^2)	1.45 ± 0.45	1.1 (0.3 – 1.4)	1.7 (1.5 – 2.4)	<0.001
Follow-up duration (year)	2.21 (0.74 – 7.83)	1.92 (0.93 – 5.38)	3.66 ± 2.19	0.133
Rate of MVA decrement (cm^2/year)	0.13 (0 – 0.62)	0.28 ± 0.14	0.02 (0 – 0.18)	<0.001
Wilkins' score	7 (5 – 9)	7.5 (5 – 8)	7 (6 – 9)	0.604
Wilkins' score ≥8 (n, %)	19 (47.5%)	10 (50%)	9 (45%)	0.752
Poor 2nd prophylaxis compliance (n, %)	9 (22.5%)	5 (25%)	4 (20%)	0.500
IL-6 level (pg/mL)	2.39 (0.03 – 11.4)	2.39 (0.03 – 11.4)	2.44 ± 1.99	0.425

Table 2. Bivariate and multivariate analysis of the association between dependent variables and mitral valve restenosis.

Variables	Bivariate Analysis		Multivariate Analysis	
	OR (CI 95%)	P value	OR (CI 95%)	P value
Female	1.29 (0.32 – 5.18)	0.723		
MVA after PTMC ≤1.8 cm^2	3.67 (0.96 – 14.03)	0.053	2.79 (0.39 – 20.04)	0.306
Rate of MVA decrement ≥0.155 cm^2/year	51 (7.57 – 343.73)	<0.001	46.72 (6.69 – 326.19)	<0.001
Wilkins' score ≥8	1.22 (0.35 – 4.24)	0.752		
Poor 2nd prophylaxis compliance	1.33 (0.30 – 5.93)	0.500		
IL-6 level ≥0.23 pg/mL	2.11 (0.18 – 25.35)	0.500		

sensitivity of 85% and specificity of 95%. IL-6 level was classified into high level (≥0.23 pg/mL) and low level (<0.23 pg/mL) based on ROC curve analysis which AUC of 0.57[4] was obtained for IL-6 level of 0.23 pg/mL with a sensitivity of 95% and 1-specificity of 90%.

In bivariate analysis, female gender, MVA after PTMC ≤1.8 cm^2, Wilkins' score ≥8, and poor secondary prophylaxis compliance were not associated with mitral valve restenosis. High IL-6 level (≥0.23 pg/mL) was not associated with mitral valve restenosis p = 0.500. The rate of MVA decrement ≥0.155 cm^2/year was associated with mitral valve restenosis with p <0.001 (OR = 51; 95% CI 7.57 – 343.73). In multivariate analysis, the rate of MVA decrement ≥0.155 cm^2/year was an independent predictor of mitral valve restenosis after PTMC with p <0.001 (OR 46.72; 95% CI 6.69 – 326.19) **(Table 2)**

Discussion

In this study, several findings were obtained: (1) Chronic inflammation assessed by IL-6 was not associated with the incidence of mitral valve restenosis after PTMC, and (2) The median MVA decrement in patients with mitral valve stenosis who underwent PTMC was 0.13 (0 – 0.62) cm^2/year, (3) The rate of MVA decrement was 0.155 cm^2/year was a predictor of mitral valve restenosis after PTMC, (4) Female gender, Wilkins' score ≥8 and MVA after PTMC ≤1.8 cm^2 were not associated with the incidence of mitral valve restenosis after PTMC, and (5) Compliance of secondary prophylaxis was not associated with mitral valve restenosis after PTMC. There was no significant difference in the levels of IL-6 between the restenosis group and no restenosis group. There was no significant difference in the incidence of mitral valve restenosis between the group with high levels of IL-6 (≥0.23 pg/mL) and the group with low levels of IL-6 (<0.23 pg/mL). Thus, chronic inflammation assessed by IL-6 was not associated with the incidence of mitral valve restenosis after PTMC. Although not statistically significant, patients with high IL-6 levels (≥0.23 pg/mL) had two times the odds of getting mitral valve restenosis compared to patients with low IL-6 levels (<0.23 pg/mL) with OR 2.11 (95% CI 0.18 – 25.35). If the sample size is large enough, study power is sufficient, and IL-6 was measured several times (i.e., in the beginning, middle, and end of the study) with a prospective study design, IL-6 is likely to be a predictor of mitral valve restenosis. Cardiac valve damage is initiated by activation and differentiation of valvular interstitial cells (VIC) into myofibroblasts caused by inflammatory processes, hemodynamic disturbances, and mechanical stress.[10] Based on pathological findings, mitral valve restenosis is caused by fibrosis of the mitral valve leaflet or sub-valvular apparatus. The balance of extracellular matrix synthesis influences this fibrosis process (e.g., collagen, elastin, proteoglycans, and matrix proteins) and extracellular matrix degradation regulated by MMP/TIMP. Mechmeche et al found that there was an increase of MMP-9 levels (292.3 ± 86.2 ng/mL vs. 155.1 ± 78.2 ng/mL, p < 0.001) and a decrease of TIMP-2 levels (117.6 ± 56.9 ng/mL vs 149.4 ± 78.9, p = 0.021) in patients with mitral valve restenosis compared to patients without mitral valve restenosis.[8] However, we did not measure the levels of MMP/TIMP, and the differences in MMP/TIMP levels could affect the incidence of mitral valve restenosis.

The MVA decrement in RHD patients with mitral valve stenosis occurs gradually. The mechanism of MVA decrement is thought to be caused by the chronic inflammatory process in RHD. Gordon et al. concluded that the mean MVA decrement in RHD patients with mitral valve stenosis was 0.1 – 0.3 cm^2/year.[14] *Song et al.* stated that the mean MVA decrement in mitral valve stenosis patients who underwent PTMC treatment was 0.03 ± 0.14 cm^2/year.[6] In our study, the median MVA decrement in mitral valve stenosis patients who underwent PTMC was 0.13 (0 – 0.62) cm^2/year. Six patients with mitral valve restenosis with a follow-up duration of about 1-2 years after PTMC had MVA decrement of 0.39 cm^2/year. Song et al. stated that mitral valve restenosis could occur within one year after PTMC with a cumulative incidence rate of about 3–5%.[6] Further analysis of the rate of MVA decrement showed that there was a relationship between the rate of MVA decrement ≥0.155 cm^2/year with mitral valve restenosis (p <0.001; OR 51; 95% CI 7.57 – 343.73). In future studies, this variable rate of MVA decrement can be used to classify patients into progressor and non-progressor groups.

RHD occurs more commonly in females, with a relative risk of 1.6 to 2.0 compared with males. The reasons for this association are unclear, but intrinsic factors such as greater autoimmune susceptibility, as

observed in systemic lupus erythematosus, and extrinsic factors such as greater exposure to GAS infection in women than in men as a result of closer involvement in child rearing might explain this difference. In addition, women and girls might experience reduced access to primary and secondary ARF prophylaxis compared with men and boys, which could also contribute to differences in RHD rates between females and males.[3] This can also be influenced by the effect of estrogen on immune cells. Lymphocytes express estrogen receptors on their cell surfaces, and activation of these receptors results in an immune response.[11] *Mechmeche et al*. stated that the female gender was not a predictor of the incidence of mitral valve restenosis after PTMC.[8] In our study, there was no significant difference in the incidence of mitral valve restenosis in the female and male groups (p = 0.723).

Wilkins' score is a scoring system used to assess the mitral valve morphology based on leaflet mobility, valve thickness, subvalvular thickening, and valvular calcification. The higher the score, the more abnormal the valve structure.[15] *Fawzy et al*. stated that Wilkins' score >8 before PTMC was a predictor of mitral valve restenosis. The mitral restenosis rate was higher in the group of patients with a Wilkins' score >8 than in the group with a Wilkins' score ≤8 during the 19-year follow-up duration.[13] *Hernandez et al*. stated that Wilkins' score >8 before PTMC was a predictor of mitral valve restenosis.[12] In our study, the median Wilkins' score was 7 (5 – 9). There was no significant difference in the incidence of mitral valve restenosis between the group with a Wilkins' score ≥8 and the group with a Wilkins' score <8 (p = 0.752).

MVA after PTMC is a predictor of mitral valve restenosis. Fawzy et al. stated that MVA after PTMC <2 cm^2 was a predictor of mitral valve restenosis.[13] *Hernandez et al*. and *Song et al*. stated that MVA after PTMC <1.8 cm^2 was a predictor of mitral valve restenosis.[6,12] In our study, the mean MVA after PTMC was 1.76 ± 0.28 cm^2 in the restenosis group and 1.92 ± 0.24 cm^2 in the no restenosis group. There was no association between MVA after PTMC ≤1.8 cm^2 and mitral valve restenosis (p = 0.053). This finding may be due to the small sample size of the study. Further research is needed with a larger sample size to assess the association of MVA after PTMC with mitral valve restenosis so that target MVA can be determined during PTMC to prevent mitral valve restenosis.

Secondary prophylaxis refers to the consistent and regular administration of antibiotic therapy in patients with a history of ARF and RHD to prevent ARF recurrence. First-line therapy is PBG. Second-line therapy is phenoxy-methyl penicillin (PMP) and erythromycin. In our study, around 77.5% of patients showed good secondary prophylaxis compliance. However, none of them received PBG as secondary prophylaxis. All of them received PMP as secondary prophylaxis. In our study, it was found that there was no significant difference in the incidence of mitral valve restenosis between patients with good compliance and poor compliance. There are several reasons explaining the results of this study. From a pharmacology aspect, blood levels of PMP were not measured. Therefore, it is unknown whether patients had achieved the minimum inhibitory concentration (MIC) for GAS. *Sika-Paotonu et al*. stated that to prevent GAS colonization and ARF recurrence, a concentration of benzylpenicillin in serum or a minimum inhibitory concentration (MIC) of >0.02 g/ml is required.[16] Also, oral penicillin is more challenging to achieve a therapeutic dose than intramuscular penicillin.[17] In our research methodology, the adherence level of secondary prophylaxis is limited by operational definition. Poor compliance was defined when the patient did not get >2 injections in the last 12 months or did not get >24 hours of oral medication in the past month. From a microbiology aspect, it is necessary to consider the possibility of penicillin antibiotic resistance in GAS. *Vannice et al*. reported 2 cases of missense pbp2x mutations in *Streptococcus pyogenes* (subtype emm 43.4). These were associated with resistance to beta-lactam antibiotics, and an increase in ampicillin and amoxicillin MIC was eight times higher than controls.[18] Further research is needed to determine the association between secondary prophylaxis and mitral valve restenosis by measuring the adherence level of secondary prophylaxis with a standardized questionnaire (e.g., Morisky Medication Adherence Scale or MMAS-8-Item) and the possibility of GAS antibiotic resistance in Indonesia.

Study Limitation

There were several limitations in this study. First, this study recruited a relatively small number of patients due

to the COVID-19 pandemic; some have a short follow-up duration. Second, IL-6 was measured once during subject recruitment; therefore, it could not describe the overall chronic inflammatory process. Third, secondary prophylaxis compliance was defined using study criteria because it is difficult to get accurate information about PMP adherence.

Conclusion

Chronic inflammation assessed by IL-6 was not associated with the incidence of mitral valve restenosis after PTMC.

Conflict Of Interest

There is no conflict of interest. This study was supported by The Excellent Research Grant of the National Cardiovascular Centre Harapan Kita (Grant number: LB.02.01/VII/440/KEP.045/2020).

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Figure 1. Hospital mortality rate in ST-ACS based on reperfusion strategies.