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Original Article

Correlation of Ischemic Time with Diastolic Dysfunction and Correlation of Diastolic Dysfunction with 6 Minute Walk Test Distance in STEMI Patients Receiving Percutaneus Coronary Intervention

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ABSTRACT

Background: Minimizing the time between ischemia and reperfusion in STEMI patients is critical for myocardial salvage and limiting residual injury. One of the methods for determining the impact of ischemic time on the myocardium and correlating the findings to the outcomes is by using echocardiography.

Objectives: To evaluate the correlation of ischemic time to diastolic dysfunction and also the correlation of diastolic dysfunction to functional capacity by 6-minute walk distance in STEMI patients.

Methods: The study was a retrospective cohort, to all STEMI patients who underwent PCI at RSUD Dr. Saiful Anwar Malang between January 2018 and November 2021. All patients underwent PCI, echocardiography, and a 6-minute walk test before being discharged. We defined significant diastolic dysfunction as grade 2 or 3 diastolic dysfunction, according to the 2016 American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) guidelines. The distance of 6-minute walk test was divided into three categories: less than 300 m, 300-400 m, and more than 400 m.

Results: From total 258 patients, 92 patients (35.7%) had significant diastolic dysfunction. The significant diastolic dysfunction was correlated with ischemic time >12 hours (r = 0.51, p <0.001), Killip class (r = 0.46, p <0.001), culprit artery (r = 0.203, p <0.001), and peak troponin I level (r = 0.35, p <0.001). We identified that the ischemic time (OR = 6.783; 95% CI = 3.266 to 14.087; p <.001), Killip class (OR = 4.629; 95% CI = 2.527 to 8.480; p <0.001), and infarct size by peak troponin I levels (OR = 1.121; 95% CI = 1.064 to 1.181; p <0.001) as independent predictors of significant diastolic dysfunction. There was inversely correlation of diastolic dysfunction with 6-minute walk test distance. (r = -0.422, p <0,001), with E/e' as independent predictors of level of 6-minute walk distance (OR = -1.126; 95% CI = -1.776 to -0.475; p = 0.001).

Conclusion: Ischemic time is one of the independent predictors of significant diastolic dysfunction. LV diastolic dysfunction was inversely correlated with 6-minute walk test distance in STEMI patient.

1. Introduction

Ischemic heart disease is a major cause of morbidity and mortality. In Europe, there were ±1.8 million deaths per year because of ischemic heart disease, with large differences between countries.1 Approximately every 40 seconds, an American will have a myocardial infarction. The prevalence of myocardial infarction is 3.1% in adults ≥ 20 years of age in the United States.[2] STEMI occurs at a rate of 43-144 per 100,000 people in Europe each year.[1] According to the Jakarta Acute Coronary Syndrome (JAC) Registry, 3015 cases of acute coronary syndrome were reported in Indonesia between October 2014 and July 2015, with 1024 cases of STEMI.[3]

STEMI reperfusion can be accomplished through the use of a fibrinolytic agent or through a percutaneous coronary intervention (PCI). The intrahospital mortality rate of STEMI that underwent PCI was 3.52%, lower than non-PCI patients, namely 14.91%.2 Minimizing reperfusion delays is critical to save the myocardial area that was ischemic, limit residual injury, lower the risk of heart failure, and improve survival in STEMI patients.[4] Large infarct area, late to hospitalization, and lack of tissue reperfusion remains a cause of mechanical complications, hemodynamic instability, and pump failure.[5]

The time required for reperfusion in STEMI patients is expected to be proportional to the degree of LV diastolic dysfunction, as determined by echocardiography. Currently, LV diastolic function is still receiving less attention than LV systolic function.[6] In fact, diastolic disturbances occur earlier than systolic disorders and can predict a poor prognosis after STEMI.[7]

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The mechanisms underlying post-infarction LV diastolic dysfunction are complicated. Following myocardial infarction, the impairment of myocardial active relaxation, as well as the stiffer LV chamber due to myocardial ischemia and/or other pathophysiological factors, are thought to cause LV diastolic dysfunction.[6]

The six-minute walk test (6MWT) is low-cost, safe, and well-tolerated method of determining a patient's functional exercise capacity.[8] The correlation between diastolic dysfunction and 6MWT distance in post-STEMI patients has never been thoroughly investigated. 6MWT also has a role in cardiac rehabilitation after STEMI. It is possible to motivate the patient to perform measurable activities at home by performing 6MWT before discharge. Physical activity has been shown to lower cardiovascular mortality by reducing hypertension, dyslipidemia, obesity, and diabetes mellitus, as well as possible effects on atherosclerosis, endothelial dysfunction, autonomic control, and the risk of subsequent arrhythmias.[9] The gold standard for determining aerobic capacity is to evaluate peak oxygen uptake by performing a test with Cardiopulmonary Exercise. However, these tests are relatively expensive and time-consuming.[8]

This study was performed to determine the correlation between the ischemic time to the degree of LV diastolic dysfunction and the correlation of the degree of LV diastolic dysfunction to the distance of 6MWT in STEMI patients who underwent percutaneous coronary intervention at dr. Saiful Anwar Malang.

2. Materials and Method

The population in this study were patients with STEMI who underwent PCI procedures at Saiful Anwar Hospital Malang from January 2018 until November 2021. The sampling technique used was consecutive sampling. The ethical committee at our hospital gave their approval to this study. Clinical information was gleaned from patient medical records. The ischemic time was assessed from the first unstable anginal symptoms until wire crossing on infarct-related artery. The ischemic time was divided into 2 groups, less than 12 hours and ≥12 hours.

The inclusion criteria were patients with STEMI diagnosis, that undergone PCI procedure, got echocardiography examination within 48 hours after PCI, and 6MWT before discharge, and have complete medical record data. Exclusion criteria were patients with a history of coronary artery disease diagnosis before hospitalization, history of PCI, history of CABG, known history of heart failure diagnosis, history of diastolic dysfunction if there is a previous echocardiography examination, received fibrinolytic therapy, very unstable hemodynamics (receiving ventilator, inotropic, IABP), TIMI flow after PCI <3, not receiving ACE inhibitor / ARB / beta blocker therapy, not receiving antihypertensive therapy in patients with a history of hypertension, anti-diabetics in patients with diabetes, and anti-dyslipidemia in patients with dyslipidemia, idiopathic cardiomyopathy, valvular heart disease (moderate-severe aortic valve stenosis/regurgitation, moderate-severe mitral stenosis/regurgitation), malignancy, severe renal and hepatic dysfunction or another uncontrolled systemic disease, has lower extremity, pulmonary disorders, or death during hospitalization.

The echocardiographic protocol was performed by cardiology resident, validated by the cardiologist consultant, and followed a standard format imaging. The 6MWT was performed by skilled nurse and validated by the cardiologist consultant. The algorithm of Left Ventricular Diastolic Function of 2016 ASE/EACVI guideline was used to grade diastolic dysfunction. Grade 1 diastolic dysfunction was defined as E/A≤ 0.80 and E wave ≤ 0.5 cm/sec and grade 3 diastolic dysfunction was defined as an E/A ratio of ≥ 2. Grade 2 diastolic dysfunction was defined as E/A ratio > 0.8 to < 2.0 (or an E/A ratio of ≤ 0.8 with E wave > 0.5 m/sec) and two of three of LAVI > 34 mL/m2, TR velocity > 2.8 m/sec, or average E/e' ratio >14. On the basis of the distance of 6MWT, performance was grouped into three different levels (level I = <300 m, level II = 300 – 400 m, and level III >400 m).

To identify clinical, laboratory, and echocardiographic parameters linked to diastolic dysfunction, researchers used univariate, bivariate, and multivariate analyses. The mean and standard deviation are used to express continuous data (SD). The chi-square test or the T-test were used to assess proportional differences. The Kendal tau b correlation coefficient was used to assess the bivariate correlations between variable and grade diastolic dysfunction. Spearman correlation coefficient was used to assess diastolic dysfunction and 6MWT distance level (r). To determine the relationship between a variable and grade diastolic dysfunction, researchers used multivariate binary logistic regression analysis. The Mann-Whitney test is used for post hoc analysis. To identify the relationship between echocardiographic parameters of diastolic dysfunction with the 6-minute walk test distance level, multivariate ordinal regression analyses were used. We used a 0.05 significance level. To conduct the statistical analyses, we use IBM Corp.'s SPSS version 26.0.

3. Results

The clinical, laboratory, and echocardiographic variables are presented in Table 1 and Table 2. From the 577 consecutive patients with STEMI, 299 patients were excluded, leaving 258 patients were included to study. The study population included mostly men (79.8%), with a mean age of 58.8 ± 11.8 years, and smoking was the most common risk factor (63.6%). Using the LV diastolic dysfunction algorithms, 166 patients (64.3 %) were classified as nonsignificant diastolic dysfunction and 92 patients (35.7 %) were classified as significant diastolic dysfunction.

Bivariate correlations of clinical, laboratory, and angiographic variables showed the correlation of diastolic dysfunction with ischemic time ≥12 hours were significant (r = 0.51, p <0.001), and also Killip class (r= 0.46, p <0.001), culprit artery (r= 0.20, p <0.001), and peak troponin I level (r=0.35, p <0.001). Multivariate analysis showed that ischemic time (OR = 6.783; 95% CI = 3.266 to 14.087; p <.001), Killip class (OR = 4.629; 95% CI = 2.527 to 8.480; p <0.001), and infarct size by peak troponin I levels (OR = 1.121; 95% CI = 1.064 to 1.181; p <0.001) had a significant effect on diastolic dysfunction level (Table 3).

There was significant difference between the level of diastolic dysfunction and the distance of 6MWT in Table 4, with a p value of <0.001. This is consistent with post hoc analysis that showed a significant difference between level of 300 m and 300-400 m (p <0.001), the 300-400 m and >400 m (p <0.001), and the 300 m and the >400 m (p <0.001). There was a moderate correlation between diastolic dysfunction and the level of 6MWT distance level (r = -0.422 and p <0.001). Based on echocardiographic parameter we found significant correlation of 6MWT distance level with E (r = -0.397, p <0.001), e' septal (r = 0.367, p <0.001), and e' lateral (r = 0.402, p <0.001) in a bivariate analysis.

4. Discussion

From a study by Tern et al. involving STEMI for 5 countries in Asia Pacific region (Australia, Japan, Korea, Singapore, and Malaysia).

Table 3.2 Baseline characteristics of subjects in each category

Variable	Significant diastolic dysfunction (n = 166)	Non Significant diastolic dysfunction (n = 92)	P-value 0.487
Age (year)	58.4 ± 10.7	59.5 13.8	0.526
Sex			
Male	135 (52.3%)	71 (27.5%)	0.294
Female	31 (12.0%)	21 (8.1%)	
Risk factors			
Obesity	12 (4.7%)	11 (4.3%)	0.421
Smoking	109 (42.2%)	55 (21.3%)	0.146
Hypertension	82 (31.8%)	36 (14.0%)	0.183
Diabetes mellitus	60 (23.3%)	25 (9.7%)	0.64
TIMI group			
Low risk	121 (46.9%)	56 (21.7%)	
High risk	45 (17.4%)	36 (14.0%)	
Grace Group			0.931
Low risk (≤108)	66 (25.6%)	35 (13.6%)	
Intermediate risk (109-140)	67 (26.0%)	37 (14.3%)	
High risk (141-140)	33 (12.8%)	20 (7.8%)	
Killip			<0.001
I	138 (53.5%)	38 (14.7%)	
II	27 (10.5%)	38 (14.7.1%)	
III	1 (0.4%)	16 (6.2%)	
Ischemic time			<0.001
<12 hours	113 (43.8%)	14 (5.4%)	
≥12 hours	53 (20.5%)	78 (30.2%)	
Physical examination and Laboratorium			
Systolic Blood Pressure	124 ± 15.1	126 ± 15.8	0.197
Heart rate	76 ± 11	77 ± 12	0.400
Haemoglobin	13.6 ± 1.66	13.5 ± 1.66	0.632
Leucocyte	12547 ± 3313	12941 ± 3484	0.377
Troponin	7.23 ± 4.6	12.7 ± 8.2	<0.001
eGFR	83.8 ± 31.3	85.6 ± 33.1	0.659
Random Blood Sugar	138 ± 32.7	138 ± 33.4	0.888
Culprit artery			0.040
LAD	52 (20.2%)	48 (18.6%)	
LCx	4 (1.6%)	2 (0.8%)	
RCA	110 (42.6%)	42 (16.3%)	
Vessel			0.892
1 vessel	31 (12.0%)	15 (5.8%)	
2 vessel	39 (15.1%)	22 (8.5%)	
3 vessel	96 (37.2%)	55 (21.3%)	

Note. LAD = left anterior descending; LCx = left circumflex; RCA = right coronary artery; TIMI = Thrombolysis in Myocardial Infarction

The average patient age was 61.6 (57.9 to 65.3), the proportion of males was 78.7 (74.6 to 82.3) %, proportion of smokers 53 (44.1 to 61.7) %, proportion of diabetes mellitus 30.5 (23.9 to 37.9) %, proportion of hypertension 53.7 (48.5 to 58.3) %.10 However, there is heterogeneity from various Asia Pacific countries. In our study, we found a similar proportion with the average age was 58.4 ± 11.8 years, the proportion of males was 78.7%, and smokers were 63.5%.

Multivariate analysis identified the ischemic time and infarct size by peak troponin I level as independent predictors of significant diastolic dysfunction. The longer the ischemic time, the more extensive the myocardial damage.[11] This is consistent with several observational studies. A study by Prasad et al. on 95 patients with a first-time STEMI showed that time from symptom to reperfusion was an independent predictor of restricted filling pattern (RFP) as well as the extent of infarct by peak troponin T level. The RFP was determined as an E/A mitral inflow ratio >2.0 and/or an E wave deceleration time (DT) <140 ms.[12] Another study by Prasad et al involved 477 patients with hospitalized first-time myocardial infarction, showed that 69 patients (14.5%) had significantly higher peak Troponin I level in the RFP group.[13]

Table 2. Baseline Characteristic of Echocardiography

Variable	Significant diastolic dysfunction (n = 166)	Non Significant diastolic dysfunction (n = 92)	P-value
Biplane LVEF	56.3 ± 3.7	55.75 ± 3.7	0.221
TAPSE	1.79 ± 0.2	1.80 ± 0.2	0.928
IVSD	9.8 ± 1.8	10.1± 1.9	0.277
LVIDd	49.7 ± 5	50 ± 5	0.609
LVPWd	10.6 ± 1.9	10.8 ± 1.6	0.348

Note. IVSD = interventricular septal diameter; LVEF = left ventricular ejection fraction; LVIDd = left ventricular internal diameter in diastole; LVPWd = posterior end-diastolic wall diastolic thicknesses; TAPSE = tricuspid annular plane systolic excursion.

Table 3. Last Step of Multivariate analysis for association of ischemic time. Killip Class. Culprit Artery. and Troponin with Diastolic Dysfunction Level

Variable	Diastolic Dysfunction		P-value
	Hazard Ratio	95% Confidence Interval	
Ischemic Time	6.783	3.266 to 14.087	<0.001
Killip	4.629	2.527 to 8.480	<0.001
Troponin	1.121	1.064 to 1.181	<0.001

Table 4. Characteristic of 6-Minute Walk Test Distance and Diastolic Dysfunction level

Variable	Diastolic Dysfunction		P-value
	Nonsignificant	Significant	
6MWT distance			
<300 m	4 (1.6%)	26 (10.1%)	0.001
300-400 m	104 (40.3%)	59 (22.9%)	
>400 m	58 (22.5%)	7 (2.7%)	

Note. 6MWT = 6 Minute walk test.

Table 5. Multivariate analysis for association of echocardiography parameter with 6MWT distance level

Variable	6MWT Distance Level		P-value
	Hazard Ratio	95% Confidence Interval	
E	0.089	-0.002 to 0.179	0.055
e' septal	-0.211	-0.682 to 0.260	0.381
e' lateral	-0.463	-0.907 to 0.036	0.070
E/e'	-1.126	-1.776 to -0.475	0.001
LAVI	0.083	-0.004 to 0.170	0.060

Note. E = early mitral inflow velocity; e' = mitral annular early diastolic velocity; LAVI = left atrial volume index.

Troponin level has been shown to correlate well with infarct size in a number of studies using MRI with late-stage gadolinium enhancement. All single cardiac Troponin T examinations in any of the first 4 days and peak cardiac TnT were found to be well correlated with infarct area.[14] Troponin as a marker of infarct area has also been demonstrated by a study using SPECT-MPI on 52 post-AMI patients. Independent predictors of measured SPECT-MPI infarct size included cardiac TnT on days 1, 2, and 3 and peak cardiac TnT, but not <12 h presentation.[15]

Killip Class was found to be an independent predictor of significant diastolic dysfunction in our study. Wang et al found that door to balloon time and Killip III or IV status were independent predictors for diastolic dysfunction among 340 STEMI patients who underwent primary PCI.[6] This is also in accordance with previous studies in AMI patients where there was a significant difference in the degree of Killip in the degree of diastolic dysfunction using the E/e' strain rate.[16]

The correlation between the level of diastolic dysfunction and the 6MWT distance level as exercise capacity was significant in our study. The higher the diastolic dysfunction level, the 6MWT distance was shorter. From the analysis of each echocardiographic parameter, the 6MWT distance significantly correlated with E, e' septal, e' lateral, E/e', and LAVI. In multivariate analysis, we identified E/e' as independent predictors of 6MWT distance level (Table 5).

This is consistent with a study conducted on 225 patients one month after an acute myocardial infarction by Frontes-Carvalho R et al., which assessed exercise capacity using peak oxygen consumption (VO2). Peak VO2 was found to be significantly related to e' septal, e' lateral, septal E/e' ratio and lateral E/e' ratio. With increasing septal E/e' ratio there was a decrease in peak VO2 in multivariate analysis.[17] The diastolic mitral inflow velocity to early diastolic mitral annular velocity (E/e') ratio was the noninvasive indicator of elevated LV filling pressure. The E/e' ratio has been shown to correlate well with LV diastolic parameters obtained using pressure-volume loop methods.[18]

This is also consistent with Grewal et al study that diastolic dysfunction is strongly inversely related to exercise capacity. The left ventricle systolic function was within normal limits. After multivariate analysis, patients with mild and also moderate/severe diastolic dysfunction had lower exercise capacity when compared to normal diastolic function. In different multivariate analyses, resting and post-exercise E/e' were both associated with reduced exercise capacity.[19]

Because patients did not have echocardiograms data of LV diastolic function prior to presenting with STEMI, pre-existing diastolic dysfunction became a significant confounding factor. Cardiopulmonary exercise testing provides the most precise measurements of exercise capacity, which can be used in future research. Our study was a single-center retrospective study, so future prospective multicenter studies about the relationship between ischemic time and diastolic dysfunction are necessary.

5. Conclusion

Ischemic time is one of the independent predictors of significant diastolic dysfunction. LV diastolic dysfunction was inversely correlated with exercise capacity assessed by 6-minute walk test distance.

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 involvement 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: IK. Design: IK. Control/supervision: AFR, MSR, SA, IP. Literature search: IK. Data extraction: IK. Statistical analysis: IK. Results interpretation:IK. Critical review/discussion: AFR, MSR, SA, IP. Writing the article: IK. 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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