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LEFT VENTRICULAR FILLING PRESSURE ASSESSED BY ECHOCARDIOGRAPHY AS A PREDICTOR OF MAYOR CARDIOVASCULAR EVENTS DURING HOSPITALIZATION IN NON ST ELEVATION MYOCARDIAL INFARCTION

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Abstract

Background : Acute myocardial infarction (AMI) was marked by regional myocardial damage that caused systolic and diastolic dysfunction, relaxation time starts to shorten with a simultaneous rise in left ventricular filling pressure (LVFP). LVFP could be obtained from echocardiographic examination and would predict adverse outcome after an AMI.

Methods: Patients were collected from December 2018 until June 2019. A cohort prospective study of 110 consecutive NSTEMI patients admitted to the emergency department was studied. Variables such as previous comorbidities, medication history, ejection fractions (EF), and laboratory findings were evaluated. Echocardiographic examination was performed within 12 hours of admission in all patients. Elevated LVFP was defined as grade II and III diastolic dysfunction. The MACE component that included in this study are mortality, heart failure, arrhytmia and cardiogenic shock. They were then further followed up. The patient who underwent MACE within hospitalization start from a day of admission was then considered positive.

Result: From total 110 patients, there were 45 (40.9%) patients who underwent MACE and heart failure was the most about 42(38.2%). There were no significant risk factor difference between both groups. From chi square analysis, there was significant statistic between LVFP and in hospital MACE (RR: 3.33, 95% CI: 1.78-6.23, p value : <0.001). We then performed logistic regression between factor that could influenced in hospital MACE with the results of statistically significant of LVFP (OR: 5.40, 95% CI: 1.79-16.28; p=0.003).

Conclusions: LVFP is a independent predictor of in hospital MACE in NSTEMI patients. Further prospective study in validating its predicting value was needed.

Introduction

Myocardial infarction is defined as a total blockage of coronary blood flow that can cause ischemia and myocardial necrosis.[1] According to the World Heart Organization (WHO) in 2013, as many as 17.5 million people died or around 31% of total deaths were caused by cardiovascular disease each year. And about 80% of all deaths are caused by heart attacks and strokes.[2]

Acute myocardial infarction causes disturbances in the left ventricle both systolic and diastolic dysfunction in the survivor. During the initial phase of myocardial infarction 38% of patients will experience relaxation disorders and 24% will experience a restrictive filling pattern of the left ventricle. The most important impact of diastolic dysfunction is an increase of left ventricular filling pressure. Left ventricular diastolic pressure increases in acute myocardial infarction as a result of myocardial edema due to ischemia causing stiffness of the ventricular wall and a decrease in left ventricular global compliance. Left ventricular diastolic dysfunction is associated with morbidity and death and is independent of systolic function in acute myocardial infarction. Left ventricular diastolic pressure is associated with increased hospital mortality in acute myocardial infarction. It is therefore necessary to assess diastolic function and left ventricular filling pressure which has important prognostic implications.[3,4]

Methods

This cohort-prospective study was conducted at the Haji Adam Malik Medan General Hospital (RSUP HAM) with permission from the Research Ethics Committee of the Faculty of Medicine, University of Sumatera Utara (FK USU)-RSUP HAM from December 2018 to June 2019. The research subjects were male and female who had been diagnosed and hospitalized with NSTEMI. Exclusion criteria were poor acoustic window, significant mitral or aortic valve disease, atrial fibrillation, paced rhytm, and ventricular tachyarrhytmia and significant hemodynamic instability (shock, acute pulmonary edema, requirement for mechanical ventilation)on admission. Comprehensive transthoracic echocardiography was performed within 12 hours of admission in all patients. All echocardiograms were obtained using MedisonAccuvix 10 with Doppler tissue imaging software and a 2.5 to 5 MHz, variable frequency, phased-array transthoracic transducer. The echocardiographic protocol followed a standard format with image acquisition from the parasternal, apical, and subcostal acoustic window and included two-dimensional, color flow mapping, continuous and pulsed wave Doppler and Doppler tissue imaging. All clinical and angiographic data were prospectively collected.

Left ventricular systolic function was assessed by left ventricular ejection fraction obtained using the biplane method from the apical four and two chamber views. Estimation of left ventricular filling pressure was defined according to the 2016 ASE/EACVI guideline using the algorithm "Assessment of Diastolic Function in Patients with Depressed LVEF or Underlying Myocardial Disease". Left ventricular filling pressures was assessed on the basis of mitral inflow data, Doppler tissue imaging at the septal and lateral mitral annulus, LAVI, and tricuspid regurgitation velocity. Mitral inflow doppler was obtained by placing a 1 mm pulsed wave sample box at the mitral leaflet tips in the apical four chamber view at the end expiration using a sweep speed of 50-100 mm/sec. Doppler tissue imaging was performed by placing a 2 mm pulsed wave sample box at the septal and lateral mitral annulus, and then the average of septal e' and lateral e' velocities was calculated (average e'). E/e' ratio was calculated using the early mitral inflow E wave velocity and septal e' (E/e' septal), lateral e' (E/e' lateral), and the average of septal and lateral e' (E/e' average). LAVI was assessed using a biplane method where left atrial endocardium was traced out in the apical four and two chamber views at the ventricular end systole just before mitral valve opening with the left atrial appendage, the area under the mitral valve annulus, and the inflow of the pulmonary veins excluded from the tracing. The calculated volume was indexed to body surface are to calculate LAVI. TRV was obtained from the maximum velocity obtainer with continuous wave Doppler echocardiography from complete traced obtained either from the parastenal long axis right ventricular inflow view or from the apical four chamber view. Color flow mapping was used to align the line of interrogation in line with the regurgitant jet. Grades of DD were defined according to the 2016 ASE/EACVI guidelines. Grade 1 DD was defined as E/A $\leq$ 0.8 and E wave < 0.5 cm/sec; grade 2 DD was recognized as an E/A ratio of 0.8 to 2.0 (or an E/A ratio $\leq$ 0.8 with E wave > 0.5 m/sec), and two of three of LAVI > 34 mL/m^2, TRV > 2.8 m/sec, or average E/e' ratio > 14; and grade 3 DD was defined as mitral inflow E/A ratio $\geq$ 2.0. Patients not meeting the criteria for grade 2 were classified as indeterminate (when only two of three criteria among LAVI, TRV, and average E/e' were available and one was positive and one negative). High left ventricular filling pressure was defined as grade 2 and 3 DD.[5,6]

Outcomes

The primary outcomes measure was a composite of major adverse cardiovascular events (MACEs), comprising all cause death, acute heart failure, malignant arrhytmia and cardiogenic shock during hospitalized.

Statistical Analysis

Processing and analysis of statistical data using statistical computer devices 'Statistical Package for Social Science '/SPSS version 22-23. (IBM United States). Categorical variables are presented as percentages and were compared using Chi Suare test, and if requirements of chi square are not met, the the Fisher test is used. Continious variables are expressed as mean ± SD using an unpaired t test if data were normally distributed or the Mann-Whitney U test if data were not normally distributed. Decision making in the categorical analytical test is taken by comparing Asymp. Significance value of Chi Square test output with critical value by 0.05 (with type I error rate = 5%). If the Asymp. Significancy Value is found <0.05 then there is a relationship between variables.

Results

In this study, 110 patients with NSTEMI were obtained who had met the inclusion and exclusion criteria. Of the 110 study subjects, the majority were male about 88 people (80%) with an average age of 56.9 ± 9.6 years. From the characteristics of risk factors found 82 people (74.5%) smoked, 78 people (70.9%) had hypertension, 42 people (38.2%) had type 2 diabetes mellitus, and 10 people (9.1%) had a family history of heart disease. From the results of echocardiographic examination, it was found that the median value of left ventricular ejection fraction was 45 (20-69) and 60 people (54.5%) were categorized as high of left ventricular filling pressure from echocardiographic examination. From laboratory tests, the mean hemoglobin value was 13.4± 2.9, the median value of Troponin I was 1.54 (0.2-32), the median CK-MB value was 67 (17-475), the median creatinine value was 1.3 (0.5-4.4) and the median value of blood sugar levels when enter 145 (80-483). From coronary angiography examinations, 12 people (10.9%) had CAD 1VD, 39 people (35.5%) CAD 2VD, 53 people (48.2%) CAD 3VD, and 6 people (5.5%) with NCA. There were MACEs as heart failure, arrhythmias, cardiogenic shock, and death occurred in 42 people (38.2%), 14 people (12.7%), 12 people (10.9%), and 5 people (4.5%). Complete data is presented in table 1

Table 1 Baseline clinical and angiographic characteristics

Variable	**n=110**
Age (years old)	56.9 ± 9.6
Sex	
Female	22 (20%)
Male	88 (80%)
Risk Factors	
Smoker	82 (74.5%)
Hypertension	78 (70.9%)
Diabetes Mellitus	42 (38.2%)
Family History	10 (9.1%)
Laboratory Finding	
Haemoglobin	13.4 ± 2.3
Creatinine	1.3 (0.5-4.4)
Troponin I	1.54 (0.2-32)
CK-MB	67 (17-475)
KGD Sewaktu	145 (80-483)
Echocardiographic Examination	
LV Ejection Fraction	45 (20-69)
LV Filling Pressure	
High	60 (54.5%)
Normal	50 (45.5%)
Coronary Angiographic	
CAD 1VD	12 (10.9%)
CAD 2VD	39 (35.5%)
CAD 3VD	53 (48.2%)
NCA	6 (5.5%)
Medication	
Aspilet	108 (98.2%)
Clopidogrel	95 (95.5%)
ACE-Inhibitor	66 (60%)
ARB	22 (20%)
Beta Blocker	101 (91.8%)
Nitrat	105 (95.5%)
Furosemide	52 (47.3%)
MRA	13 (11.8%)
Statin	110 (100%)

Anticoagulant	
Enoxaparin	10 (9.1%)
Fondaparinux	82 (74.5%)
UnfractionedHeparine	15 (13.6%)
None	3(2.7%)
Inotropic	20 (18.2%)
MACEs	
Acute Heart Failure	42 (38.2%)
Arrhytmia	14 (12.7%)
Cardiogenic Shock	12 (10.9%)
All cause mortality	5 (4.5%)

Of 110 study subjects, 45 people (40.9%) experienced MACEs with an average age of 60±9.7 years and the majority were male about 35 people (77.7%), 30 people (66.7%) with history of hypertension, 31 people (68.8%) with history of smoker, 16 people with diabetes mellitus (35.5%), and 3 people (6.7%) with a family history of heart disease. From the bivariate analysis between the characteristics of patients with MACEs, we found differences in the mean age of 60 ±9.7 years (p = 0.003), troponin I 2.3 (0.31-32) (p = 0.004), CK-MB 78 (18-475) (p = 0.016)). We also found in the group of patients with MACEs were found to use drugs such as diuretics, aldosterone antagonists (MRA), and more inotropic use during treatment compared to the group of patients without MACEs (p value <0.001) (Table 2).

Table 2 Baseline Clinical Characteristics based on MACEs

Variable	**MACEs**		**P value**
	Yes (n=45)	**No (n=65)**	
Age	60 ± 9.7	54 ± 8.9	0.003*
Sex			
Female	10 (22.3%)	12 (18.4%)	0.808**
Male	35 (77.7%)	53 (81.6%)	
Smoker	31 (68.8%)	51 (78.4%)	0.363**
Hypertension	30 (66.7%)	48 (73.8%)	0.547**
Diabetes Mellitus	16 (35.5%)	26 (40%)	0.786**
Family History	3 (6.7%)	7 (10.7%)	0.690**
Laboratory Finding			
Haemoglobin	12.9 ± 2.3	13.7 ± 2.4	0.101*
Creatinine	1.5 (0.5-4.4)	1.1 (0.65-2.73)	0.120#
Troponin I	2.3 (0.31-32)	1.2 (0.2-17.8)	0.004#
CK-MB	78 (18-475)	64 (17-152)	0.016#
Blood glucose	161 (81-483)	136 (80-432)	0.296#
Coronary Angiographic			
CAD 1VD	1 (2.2%)	11 (16.9%)	0.001**
CAD 2VD	11 (24.4%)	28 (43.1%)	
CAD 3VD	32 (71.1%)	21 (32.3%)	
NCA	1 (2.2%)	5 (7.7%)	
Medication			
Aspilet	44 (97.7%)	64 (98.4%)	0.794**
Clopidogrel	43 (95.5%)	62 (95.3%)	0.966**
ACE-Inhibitor	28 (62.2%)	38 (58.4%)	0.692**
ARB	10 (22.2%)	12 (18.4%)	0.629**
Beta blocker	43 (95.5%)	58 (89.2%)	0.304**
Nitrat	41 (91.1%)	64 (98.4%)	0.157**
Diuretic	39 (86.7%)	13(20%)	<0.001**
MRA	11 (24.4%)	2 (3%)	<0.010**

Inotropic	19 (42.2%)	1 (1.5%)	<0.001**
Anticoagulant			0.134**
Enoxaparin	5 (11.1%)	5(7.7%)	
Fondaparinux	29 (64.4%)	53 (81.5%)	
UFH	10 (22.2%)	5 (7.7%)	
None	1 (2.2%)	2 (3.1%)	
Risk Stratification			
Grace Score			
>140	14 (31.1%)	1 (1.5%)	<0.001**
109-140	26 (57.7%)	24 (36.9%)	<0.001**
<108	5 (11.1%)	40 (61.5%)	

*T-test **Chi-square #Mann-Whitney

From the bivariate analysis between echocardiographic examination characteristics and MACEs, there were found median differences in the value of left ventricular ejection 40 (20-64) (p <0.001), median E / A 2.1 (0.7-3.3) (p <0.001), median left atrial volume index 34 (20-42) (p <0.001), median average E / e '15 (7.3-31.5) (p <0.001) and median maximum tricuspid regurgitation velocity 2.9 (1.5-3.4) (p <0.001) at groups that experienced MACEs. Complete data is presented in table 3

Table 3 Echocardiographic Characteristic Based on MACEs

Echocardiographic Variable	**MACEs**		**P value**
	Yes (n=45)	**No (n=65)**	
Left Ventricular Ejection Fraction	40 (20-64)	50 (28-69)	<0.001#
E/A	2.1 (0.7-3.3)	1.0 (0.4-2.23)	<0.001#
Left Atrial Volume Index	35 (20-42)	30 (18-38)	<0.001#
Average E/e’	15 (7.2-31.5)	10 (5.5-19.5)	<0.001#
TR Vmax Velocity	2.9 (1.5-3.4)	2.1 (1.0-3.2)	<0.001#
LVEDD	54 (52-57)	48 (47-50)	<0.001#
LVEDS	42 (14-60)	33 (14-56)	<0.001#
IVSD	11 (7-16)	11 (6-18)	0.236#
IVSS	13 (8-19)	14 (8-21)	0.037#
LVPWD	11 (7-16)	11 (7-20)	0.154#
LVPWS	13 (8-18)	14 (9-27)	0.002#

*T-test **Chi-square #Mann-Whitney

Based on the results of echocardiographic examinations that have been carried out on 110 patient samples, left ventricular filling pressure grouped based on ASE / EACVI guidelines on evaluating left ventricular diastolic function based on echocardiography found 60 samples (54.5%) with an increase in left ventricular filling pressure and 50 samples (45.5%) with normal left ventricular filling pressure. From the bivariate analysis test results between the left ventricular filling pressure to the incidence of MACEs obtained 36 samples (80%) with an increase of the left ventricular filling pressure who experienced MACEs and in 50 people with normal left ventricular filling pressure, found 9 samples (20%) experienced MACEs with a p value<0.001 with a relative risk value (RR = 3.33; CI95% (1.78-6.23)) (Table 4).

Table 4 Left Ventricular Filling Pressure Assessed by Echocardiography and MACEs During Hospitalized

Left Ventricular Filling Pressure	**MACEs**		**P value**	**Relative Risk**
	Yes (n=45)	**No (n-65)**		
High	36 (80 %)	24(36.9 %)	<0.001	3.33 (1.78-6.23)
Normal	9(20%)	41(63.1 %)		

Multivariate analysis test was carried out on factors related to the occurrence of MACEs during hospitalization. From the results of multivariate analysis found that the pressure of the left ventricular filling from echocardiography has a significant relationship with MACEs during hospitalization with p value = 0.003 (Table 5). The OR value for left ventricular filling pressure for the occurrence of MACEs is 5.40 (95% CI (1.79-16.28)) which indicates that left ventricular filling pressure will increase the risk of developing MACEs during hospitalization by 5.40 times higher compared to patients who have normal left ventricular filling pressure.

Table 5 Multivariate Analysis Factors Associated with In Hospital MACEs

Variable	**OR (95% CI)**	**Nilai p**
Age	1.186 (1.1-8.1)	0.671
Echocardiography		
Left ventricle ejection fraction	1.41 (0.44-4.47)	0.553
Left ventricle filling pressure	5.40 (1.79-16.28)	0.003
Grace Score		
	20 (2.63-200)	0.005
Coronary angiography	2.12 (1.78-5.63)	0.632

Discussion

Acute myocardial infarction is characterized by regional myocardial muscle damage which can cause systolic and diastolic dysfunction with the risk of left ventricular remodeling, activation of local and systemic neurohormonal systems and vascular dysfunction. Echocardiography as one of the most important modalities in acute situations which is widely available and can be carried out rapidly has significant uses in diagnosis and management and can also be used for risk stratification and prognosis in patients with acute coronary syndrome.[7,8]

In this study we found about 40.9% of the study sample experienced MACEs where the most common events were acute heart failure (38.2%), arrhythmias (12.7%), cardiogenic shock (10.9%) and death (4.5%). This is in accordance with research conducted by Haque 2001 where the most complications of acute myocardial infarction were heart failure around 53% and arrhythmia around 27%.[9] Heart failure is a frequent complication of NSTEMI and even in mild heart failure associated with increased mortality, so in patients with class Killip II and above should be classified as patients with high risk, the condition of heart failure should be considered to obtain a more invasive strategy beginning.[10]A study conducted by Kobayashi et al., 2015 in IMANEST patients found that patients with left ventricular diastolic pressure> 22 mmHg were associated with 22% heart failure (p value: 0.034) and 4% death (p value: 0.029) during treatment compared to left ventricular filling pressure <22 mmHg.[4]

Research that was conducted by Prasad et al., 2016 shows that assessment of left ventricular filling pressure based on 2016 diastolic parameter guidelines shows that patients with acute myocardial infarction with increased of left ventricular filling pressure (2/3 degree diastolic dysfunction) are strongly associated with major cardiovascular events for 2 years follow up with HR 3.37 (1.94-5.84) p value: <0.001. In this study, an increase of left ventricular filling pressure was associated with major cardiovascular events during treatment with RR 3.33 (1.78-6.23) with a p value: <0.001.[11]

An increase of left ventricular filling pressure with both direct and indirect measurements is associated with an increased risk of death. Although the prevalence and disturbance of filling are related to the degree of systolic dysfunction, the underlying finding is that there is an increase in the sign of left ventricular filling with Doppler examination, although there is only a slight decrease in left ventricular ejection. Patients with acute myocardial infarction who experience an increase in left ventricular filling pressure immediately after the occurrence of acute myocardial infarction have a worse risk burden and tolerance of acute loss of myocardial muscle ability.

Acute coronary thrombosis is the most common cause of acute myocardial infarction. This myocardial ischaemia causes damage to the myocardium and initiates an inflammatory response. The acute effects of hemodynamic myocardial infarction are amplified by structural and functional changes in the infarct and myocardial regions and by neurohormonal and inflammatory responses. Heart systolic and diastolic disorders and increased left ventricular filling pressure with pulmonary and systemic congestion can cause symptoms of heart failure and increase the risk of other cardiovascular events such as arrhythmia and death.[12]

Echocardiography as one of the most important modalities in acute situations which is widely available and can be carried out rapidly has significant uses in diagnosis and management and can also be used for risk stratification and prognosis in patients with acute coronary syndromes. In patients with acute coronary syndrome who experience an increase in left ventricular diastolic end pressure it can cause early closure of the aortic valve. If there is a decrease in the volume of the stroke, a decrease in blood flow at the systolic end can occur, which can induce a rounded aortic valve at the systolic end. In a condition where there is an increase in left ventricular diastolic end pressure which reflects the occurrence of diastolic dysfunction usually associated with more extensive infarction, and the presence of restrictive patterns associated with unexpected events.[13] Left ventricular systolic and diastolic function evaluated by echocardiographic examination can predict cardiovascular events in acute coronary syndromes. And about 70% of patients with acute coronary syndrome are classified as NSTEMI and are associated with worse long-term events 10 years after infarction. Several factors are associated with this, including an increase in the prevalence of multi-blood vessels, with a greater tendency for ischemic residuals and the presence of other comorbidities such as diabetes and chronic kidney disease.[14,15]

Conclusion

Based on the results of data analysis obtained in this study, it can be concluded that the left ventricular filling pressure in NSTEMI patients can be used as a predictor for MACEs during hospitalization

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