

Correlation between MMP-9 Level and Diastolic Dysfunction in Concentric Left Ventricular Hypertrophy Patients

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Abstract

Objective: To establish the relationship between plasma matrix metalloproteinase (MMP)-9 levels and diastolic functional abnormalities using the E/e' measurement in concentric type Hypertensive Heart Disease (HHD) patients.

Methods: A cross-sectional study was conducted from November 2014 to January 2015 in population with hypertension and concentric Left Ventricular Hypertrophy (LVH). Diastolic function was assessed with E/e' measurement using echocardiography. The relationship between the two variables was analyzed using Spearman correlation.

Results: Thirty-nine subjects (14 males, 35.9%) with the average relative wall thickness of $0.7(\pm 0.15)$, average body weight of $63.45 (\pm 12.97)$ kg, average height of $155.51 (\pm 7.12)$ cm, average body mass index of $26.23 (\pm 5.08)$ kg/m², and mean age of $55 (\pm 10)$ years were fit to be included in the analysis. The median systolic blood pressure was 140 (110–220) mmHg while the median diastolic blood pressure and median left ventricular mass index were 80 (70–110) mmHg and 119.24 (103.05–205.69) g/m², respectively. The median MMP-9 was measured at 108 (4–460) ng/mL and the median E/e' was 10.99 (6.2–20.42). There was a significant positive correlation between MMP-9 and E/e' ($r=0.416$, $p=0.004$).

Conclusion: There is a significant moderate positive correlation between the MMP-9 level and diastolic dysfunction in concentric LVH patients.

Keywords: Diastolic dysfunction, hypertensive heart disease, left ventricular hypertrophy, matrix metalloproteinase-9

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Introduction

Hypertension is a major risk factor for coronary artery disease (CAD), stroke, and heart failure.¹ The risk of heart failure in hypertensive patients is threefold higher than those without hypertension.² Hypertension is one of the most prevalent diseases in the world. The prevalence of hypertension in >25-year-old worldwide is 40.6% in men and

35.8% in women. The prevalence varies based on geographical location as well. In Southeast Asia, the prevalence of hypertension is approximately 37.3% in men and 34.9% in women.³ Based on the 2013 Indonesia Basic Health Research (Riset Kesehatan Dasar/ RISKESDAS), the prevalence of hypertension is 25.8%, with West Java sits on one of the top four most prevalent province with hypertension in Indonesia.⁴

Non-communicable diseases contributed to 63% of mortality worldwide in 2008 (36 out of 57 million deaths), mostly caused by cardiovascular diseases.⁵ Hypertension is One of many major cardiovascular disease risk factors. In Indonesia, hypertension related to 20-25% of all coronary artery disease cases

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and 36-42% of all strokes.⁶

Prolonged hypertension may injure the cardiovascular system, with secondary damages to the brain, eyes, and kidneys. The presence of target organ damage can also impact therapeutic strategies, targeted blood pressure, and specific recommended medications.^{1,7} Chronic hypertension may lead to remodeling of the heart. Cardiac remodeling involves changes in genomic, cellular, and interstitial levels that can be clinically evaluated as alterations of the heart's shape, size, and function.⁸ Concentric hypertrophy is the most common pattern of hypertrophy found in hypertension.⁸ Cardiac remodeling may also affect the heart physiology and is manifested as diastolic dysfunction. Gold standard assessment of diastolic function involves invasive measurement, but recently has been replaced by non-invasive techniques, with one of the methods is echocardiography.⁹ The method for assessing diastolic dysfunction recommended by the European Society of Cardiology (ESC) is the examination of the ratio between trans mitral inflow Doppler and Tissue Doppler Imaging (TDI) early diastolic velocity (E/e'). E/e' ratio of ≥ 13 was related to increased risk of cardiovascular event and was independent of left ventricular mass and relative wall thickness in hypertensive patients.^{7,10}

Plasma matrix metalloproteinase (MMP)-9 is one of the collagen turnover markers that is widely used as an indicator of ventricular remodeling in cases of heart failure.¹¹⁻¹³ There is a lot of studies done about MMP-9 and ventricular remodeling, both in pre-clinical studies and clinical studies. However, there are not many studies on the relationship of diastolic dysfunction with MMP-9 and these studies have had different results in terms of the relationship between MMP-9 levels and diastolic function abnormalities. This study aims to analyze the relationship between MMP-9 levels and diastolic function abnormalities.

Methods

A cross-sectional study was conducted in Bandung from November 2014 to January 2015 with ethical clearance from dr. Hasan Sadikin General Hospital. The subjects in this study included patients clinically diagnosed with concentric-type left ventricular hypertrophy HHD, age >18 years old in Out-Patient Department dr. Hasan Sadikin General Hospital. Consecutive sampling was used. The sample size (n) in this correlation

analysis study was determined by the sample and power calculation program with the calculation of the test for one correlation. The minimum number of samples that must be obtained is 30 samples. Exclusion criteria include patients with atrial fibrillation, aortic stenosis, CAD, diabetes mellitus (DM), cancer, hypertrophic obstructive cardiomyopathy, mitral stenosis, coarctation of the aorta, chronic kidney disease (CKD) stage ≥ 3 , and septic shock.

The independent variable of this study is the MMP-9 plasma level, while the dependent variable is diastolic dysfunction (E/e'). MMP-9 levels were assessed from peripheral venous blood sampling on the same day of echocardiography examination. The blood was drawn and put into a tube containing Ethylene-Diamino-Tetraacetic Acid (EDTA) and then centrifuged at 4°C . Plasma component was isolated and kept frozen at -70°C for further storage. MMP-9 plasma levels were examined using Enzyme-Linked Immunosorbent Assay (ELISA), expressed in ng/mL units.¹⁴ Diastolic dysfunction was assessed by echocardiography using a Vivid 7 echocardiography machine. Parameters were measured using the mitral inflow ratio to tissue Doppler imaging method or the E/e' ratio. E/e' values parameter is obtained from the mean values of E/e' septal and E/e' lateral.^{7,10}

A standard echocardiographic examination is performed by a technician. The results were then confirmed by a cardiologist specialized in echocardiography. Blood samples were drawn after echocardiographic examinations on the same day by trained nurses using a tourniquet and 3cc syringes. All samples were stored collectively at the Hasan Sadikin Hospital Clinical Pathology Laboratory and MMP-9 levels were assessed together on February 15, 2015.

For statistical analysis, we do a normality test using the Saphiro-Wilks or Kolmogorov Smirnov test, followed by descriptive statistics and correlation test analysis between plasma MMP-9 levels and the degree of diastolic dysfunction using Pearson product-moment correlation analysis if data is normally distributed, or with Rank Spearman if the data is not normally distributed. Confounding variables that cannot be excluded will be analyzed through multivariate analysis.

This study has been approved by Dr. Hasan Sadikin Bandung hospital's Health Research Ethic Committee number LB.04.01/A05/EC/019/I/2015.

Results

Forty-six subjects met the inclusion criteria, and seven subjects were excluded with the following causes: 1 have incomplete data (no lateral E/e' data); 1 has CAD and DM; 4 have DM; 1 has CKD stage 3. The total number of research subjects was 39 people who were involved in the data processing.

In Table 1, there are 39 samples included in the study. The normality test done on numerical data was Shapiro-Wilk test because $n \leq 50$. Normality tests show that the data on variables relative wall thickness, age, weight, height, and body mass index are normally distributed, whereas left ventricular mass, systolic blood pressure, and diastolic blood pressure were not normally distributed.

There are 14 male subjects in this study (35.9%) with 25 females (64.1%). The average age of the subjects was 55 (± 10) year, the average weight was 63.45 (± 12.97) kg, mean height was 155.51 (± 7.12) cm, mean body mass index 26.23 (± 5.08) kg/m², and average wall thickness was 0.7 (± 0.15). Median systolic blood pressure was 140 (110-220) mmHg, median diastolic blood pressure was 80 (70-110) mmHg, and the median left ventricular mass index was 119.24 (103.05-205.69) g/m².

The median value of plasma MMP-9 levels in this study was 108 (4-460) ng/mL

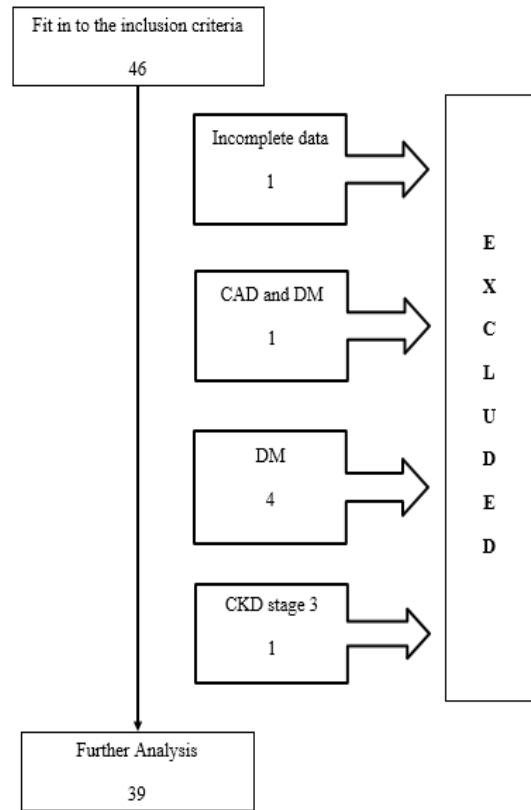


Fig. 1 Process Flow of Obtaining Research Samples

Table 1 Basic Characteristics of HHD Patients

Characteristics	Mean (\pm SD)	Median (min-max)	n (%) (n = 39)
Age (years)	55 (± 10)		
Sex (male)			14 (35.9)
Weight (kg)	63.45 (± 12.97)		
Height (cm)	155.51 (± 7.12)		
Body mass index (kg/m ²)	26.23 (± 5.08)		
Systolic blood pressure (mmHg)		140 (110-220)	
Diastolic blood pressure (mmHg)		80 (70-110)	
Left Ventricle mass index (g/m ²)		119.24 (103.05-205.69)	
Male		117.5 (115.03-146.9)	
Female		122.03 (103.05-205.69)	
Relative wall thickness	0.7 (± 0.15)		
Left Ventricular Ejection Fraction	72.62 (± 8.537)	73 (56-88)	

SD: Standard Deviation

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Table 2 Median Value of Plasma MMP-9 and E/e'

Parameters	Median (min.-max.)
Plasma MMP-9 level (ng/mL)	108 (4-460)
E/e'	10,99 (6.2-20.42)

Table 3 Correlation between plasma MMP-9 level and E/e'

Parameter	Coefficient correlation (r)	P-value
MMP-9 — E/e'	0.416	0.004

Note: Correlation analysis uses Rank Spearman correlation analysis, significant if $P < 0.05$

and the median value of E/e' was 10.99 (6.2-20.42) (Table 2).

The correlation analysis between plasma levels of MMP-9 and E/e' was shown in Table 3 and Fig. 2, presented in a scatter plot.

Based on the data elaborated above, we can conclude that the MMP-9 plasma level is moderate-positively correlated with E/e' parameter, with r value=0.416 and p=0.004 (< 0.05).

Discussion

The median left ventricular mass index in this study was 119.24 (103.05-205.69) g/m², which

is smaller than a similar study conducted by Ahmed *et al.*¹⁵ (162±6 g/m²), but greater than that of Tayebjee *et al.*¹⁶ The difference between this study and those studies may be due to the differences of inclusion criteria and the criteria for left ventricular hypertrophy used. This study used left ventricular hypertrophy criteria based on ASE and EAE guidelines, which are 115 g/m² for males and 95 g/m² for females for left ventricular mass index.¹⁰

Plasma MMP-9 median level in this study was 108 (4-460) ng/mL. Other studies have had differing MMP-9 levels and these differences may occur due to differences in the testing technique used.

This study revealed MMP-9 plasma levels were positively correlated with E/e', which means that the higher the plasma levels of MMP-9, the higher the E/e' value. This concludes that MMP-9 plasma levels are positively correlated with diastolic dysfunction in concentric HHD patients.

The association of MMP-9 level with left ventricular function has been under extensive studies. MMP-9 level relationship with left ventricular systolic function in post-myocardial infarction patients and low ejection fraction-heart failure have been widely investigated, but few studies have looked at the association of MMP-9 with diastolic function.

In previous studies done on this topic, the relationship between MMP-9 plasma levels and diastolic function is still controversial.

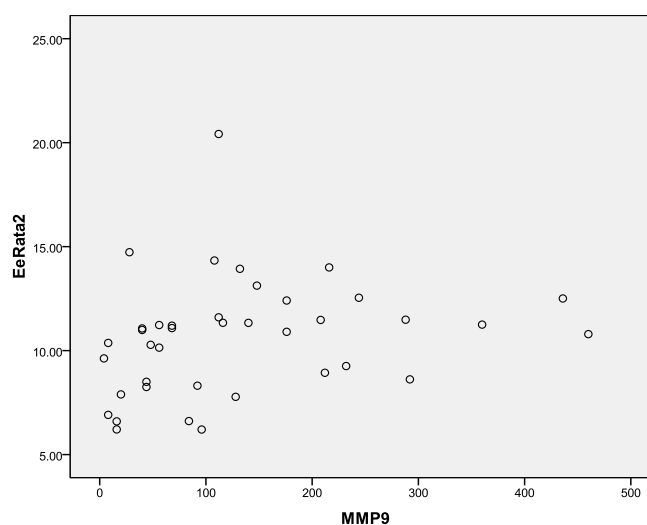


Fig. 2 Correlation between Plasma MMP-9 Levels and Diastolic Dysfunction as Measured by the E/e' test

This study result is supported by Ahmed *et al.*¹⁵ and Martos *et al.*¹⁷ studies, with the result of a significant relationship between MMP-9 levels and diastolic dysfunction. This study is not supported by the result of the study conducted by Tayebjee *et al.*¹⁶ who stated that there was no significant relationship between MMP-9 levels and diastolic dysfunction.

The coefficient correlation (*r*) between MMP-9 and E/e' in Tayebjee, *et al.*¹⁶ was -0.115, which did not statistically significant (*p*=0.349). Unfortunately, studies conducted by Ahmed *et al.*¹⁵ and Martos *et al.*¹⁷ did not mention the coefficient correlation between MMP-9 and E/e'.

The difference of results in the study by Tayebjee *et al.*¹⁶ and this study may be caused by the differences in the study population. The study of Tayebjee *et al.*¹⁶ compared all hypertensive patients with or without left ventricular hypertrophy, whereas in this study, the population is patients with a more specific left ventricular hypertrophy, which is the concentric type of left ventricular hypertrophy.

A process that may explain the increase in plasma MMP-9 levels in patients with HHD with diastolic dysfunction is described by Martos *et al.*¹⁷. Matrix Metalloproteinase-9 has collagen and extracellular matrix (ECM) turnover activity. Changes in cardiac ECM have an extensive role in terms of ventricular

contraction function, both systolic and diastolic. High levels of MMP-9 cause a high turnover of collagen which is the main component of ECM. Among these collagens, there is elastin which functions to maintain the flexibility of the heart muscle. One of the activities of MMP-9 is to activate elastase which causes an increase in elastin degradation. The loss of elastin in the heart muscle and blood vessels causes stiffness of the heart and blood vessels that contribute to an increase in the degree of diastolic dysfunction. Matrix Metalloproteinase-9 also has a profibrotic effect, which means that the increasing levels of MMP-9 will increase the occurrence of fibrosis processes which will also increase the stiffness of the heart muscle and blood vessels, thus worsening the degree of diastolic dysfunction.¹⁷

The limitation of this study is that most of the exclusion criterias were obtained from the patient's history with only a small part of the study sample had the results of diagnostic examinations, thus allowing for information bias.

In conclusion, there is a moderate positive correlation between plasma MMP-9 levels and diastolic function abnormalities as measured by E/e' examination in concentric HHD patients. Further study is needed to compare the normal population and the population with diastolic dysfunction to determine the cut-off value of MMP-9 levels in diastolic dysfunction.

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