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Difference in Correlation Coefficient between Heart Rate Variability and Mechanical Dispersion in Breast Cancer Patients with and without Cardiovascular Risk Factors Post Anthracycline Chemotherapy

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ABSTRACT

Background: Sympathetic hyperactivity is one of the several factors that influence left ventricular dyssynchrony post anthracycline. Cardiovascular risk factors affect the acceleration of left ventricular dyssynchrony. The purpose of this study is to assess the difference in correlation coefficient between HRV and mechanical dispersion in breast cancer patients with and without cardiovascular risk factors after anthracycline administration.

Method: This was a cross sectional study with linear regression analysis conducted at Hasan Sadikin General Hospital Bandung between July-October 2018. Subjects were breast cancer patients who had received 6 cycles of FAS and were divided into 2 groups. Group I was patients with breast cancer who have cardiovascular risk factors and group II was without cardiovascular risk factors. Sympathetic hyperactivity was assessed using HRV baseline frequency with minimum duration of recording and left ventricular dyssynchrony was assessed using MD method by echocardiography.

Result: This study involved 66 patients. Group I (n=34, age 50.3±6.3 years) and group II (n=32, age 48.5±9 years). The median of LF/HF ratio was 2.7 ms2 (group I) and 1.9 ms2 (group II). MD value in group I and group II was 52.2±13.6 ms and 45.7±8.8 ms, respectively. The result of linear regression analysis showed positive correlation between the LF/HF ratio and MD in group I (r=0.546, p=0.001) and group II (r=0.423, p=0.016) after adjusting three confounding factors (systolic blood pressure, cumulative dose of Doxorubicin, and age).

Conclusion: Correlation coefficient of HRV with mechanical dispersion in post anthracycline breast cancer patients in those with cardiovascular risk factors was worse compared to those without cardiovascular risk factors but was not statistically significant.

INTISARI

Latar Belakang: Hiperaktivitas simpatis merupakan salah satu faktor yang mempengaruhi disinkroni ventrikel kiri pasca antrasiklin. Faktor risiko kardiovaskular mempengaruhi percepatan disinkroni ventrikel kiri. Tujuan penelitian ini untuk menilai perbedaan koefisien korelasi HRV dengan dispersi mekanik pada penderita kanker payudara yang memiliki dan tanpa faktor risiko kardiovaskular pasca kemoterapi antrasiklin.

Metode: Penelitian ini merupakan penelitian potong lintang dengan analisis regresi linier dilakukan di RSUP dr.Hasan Sadikin Bandung bulan Juli-Oktober 2018. Subjek penelitian adalah penderita kanker payudara pasca kemoterapi dengan regimen FAS 6 siklus. Penelitian ini akan membagi dua grup. Grup I yaitu penderita kanker payudara yang memiliki faktor risiko kardiovaskular dan grup II yaitu penderita kanker payudara tanpa faktor risiko kardiovaskular. Hiperaktivitas simpatis dinilai dengan HRV berbasis frekuensi dengan perekaman jangka pendek dan disinkroni ventrikel kiri dinilai menggunakan ekokardiografi dengan metode dispersi mekanik.

Hasil: Penelitian ini melibatkan 66 penderita kanker payudara pasca kemoterapi regimen FAS 6 siklus yang dibagi dalam dua grup, yaitu grup I (n=32, usia50,3±6,3 tahun) dan grup II (n=32, usia48,5±9 tahun). Nilai median parameter rasio LF/HF = 2,7 ms2 (grup I) dan 1,9 ms2 (grup II). Nilai dispersi mekanik pada grup I = 52,1±12,2 ms dan grup II= 45,7±8,8 ms. Hasil analisis regresi linier menunjukan adanya korelasi positif antara rasio LF/HF dan dispersi mekanik di grup I (r=0,564, p=0,001) dan grup II (r=0,423, p=0,016) setelah mengontrol 3 variabel perancu (tekanan darah sistolik, dosis kumulatif doksorubisin, dan usia).

Kesimpulan: Terdapat perbedaan koefisien korelasi heart rate variability dengan dispersi mekanik pada penderita kanker payudara pasca kemoterapi antrasiklin antara yang memiliki dan tanpa faktor risiko kardiovaskular pasca kemoterapi antrasiklin, namun tidak berbeda signifikan secara statistik.

Kata Kunci: Kanker payudara, Kardiotoksisitas, Faktor Risiko Kardiovaskular, Heart Rate Variability, Dispersi Mekanik.

Introduction

Breast cancer is a malignancy that often occurs in women both in the world and in Indonesia. The use of anthracyclines could cause cardiotoxicity such as left ventricular dyssynchrony through induction of oxidative stress, inhibition of topoisomerase enzymes, and increase of death receptors.[1-3] This will reduce the performance of heart muscle and trigger hyperactivity of sympathetic nerves.[4,5]

Sympathetic nerve hyperactivity is one of several conditions that will cause myocyte remodeling and disrupt excitation-contraction coupling, which are among the causes of left ventricular dyssynchrony, a condition characterized by contraction heterogeneity in each segment of the heart muscle at one time that has the potential for heart failure.[6] Acceleration of cardiotoxicity is influenced by cardiovascular risk factors.[7]

Heart rate variability (HRV) is a good and easy method to assess the hyperactivity of sympathetic nerves. Mechanical dispersion is one of the best and accurate methods for assessing left ventricular dyssynchrony using echocardiography with speckle tracking echocardiography technique. Studies investigating the relationship between HRV and mechanical dispersion in breast cancer patients with or without cardiovascular risk factors after completion of anthracycline chemotherapy have not been found in the existing literature.

Methods

Study population

Breast cancer patients older than 18 years old who received 6 cycles FAS regiment chemotherapy, that comprises of both adjuvant and neoadjuvant in RSUP Dr. Hasan Sadikin Bandung was enrolled. The study was conducted from July to October 2018. The subject was divided into Group I and Group II. Group I was classified as subject with cardiovascular risk factors associated with cardiotoxicity, including: hypertension, diabetes mellitus, hypercholesterolemia, smoking, obesity, coronary artery disease, heart valve disease, and cardiomyopathy. Group II was subject without cardiovascular risk factors. Exclusion criteria in this study include: poor echocardiography window, rhythm other than normal sinus rhythm, hypertensive heart disease, chronic obstructive pulmonary disease, stroke, acute coronary syndrome, acute and chronic heart failure, and a history of radiotherapy.

Mechanical Dispersion and Heart Rate Variability

Mechanical Dispersion was assessed using global longitudinal strain method with a speckle tracking echocardiography technique that was calculated from the Q/R waves on the electrocardiography to each systolic peak of each segment of the heart muscle. Echocardiography was analyzed by 1 cardiologist who is an expert in the field of echocardiography. Heart Rave Variability used frequency-based which is assessed in a short recording period of 30 minutes. The electrophysiology test used the holter Kenz Cardy 302 Max, so that the parameter is LF/HF ratio. The data was recorded as a ratio (numeric data). Examination is performed 24 hours after administration of 6 cycles of chemotherapy.

Statistical Analysis

Statistical analysis was carried out using SPSS version 23. This study used bivariate analysis and continued with linear regression analysis. Normality of numerical variables was tested using the Shapiro-Wilks test. Normally distributed data was presented in mean and standard deviations while non-normally distributed data was presented in median and minimum-maximum range. The Pearson correlation coefficient was calculated to assess the magnitude of the correlation between HRV and mechanical dispersion in each group. If the calculation assumption of the Pearson correlation coefficient was not met, Spearman correlation coefficient will be calculated. All statistical tests was carried out at the 5% significance level.

Results

Total subjects were 34 people in group I and 32 people in group II. Eight patients from a total of 74 people were excluded on the grounds that 2 people refused to participate, 3 people had a history of radiotherapy, and 3 people had a poor echo window. In Group I, the mean age was 50.2±6.2 years. The mean cumulative dose of doxorubicin was 555.9±54.4 mg/m2 and the median ejection fraction was 60%. The mean body mass index was 25.6± 4.1 kg/m2 and 9 subjects were categorized as obese. Seventeen subjects were categorized as hypertension with a median systolic blood pressure of 135 mmHg and a diastolic blood pressure of 85 mmHg. Twenty-one study subjects had dyslipidemia with a median total cholesterol of 215.5 mg/dl. Research subjects who had diabetes mellitus were 2 people with a median of fasting blood sugar 98 mg/dl. Group I subjects who smoked as much as 1 person. The creatinine mean was 0.76±0.12 mg/dl and the median glomerular filtration rate was 93.4 mL/min/1.73m2. In Group I, there were no cardiovascular risk factors such as coronary artery disease, cardiomyopathy, and heart valve disease. In Group II, the mean age was 48.5±9 years, the mean cumulative dose of doxorubicin was 578±43.8 mg/m2, and the median ejection fraction was 64%. The subjects in Group II have a median weight of 63.5 kg and the mean body mass index was 25.1±2.3 kg/m2. The median systolic blood pressure is 120 mmHg and diastolic blood pressure is 80 mmHg. Laboratory tests showed median total cholesterol of 168 mg/dl, fasting blood sugar 91.5 mg/dl, creatinine 0.77±0.13 mg/dl, and glomerular filtration rate of 96.5 mL/min/1.73m2.

Table 1
Baseline Characteristic

Characteristic	Group I n= 34	Group II n= 32	P *Value*
Age (year), mean (SD)	50.2±6.2	48.5±9	0.081[a]
Cumulative dose of doxorubicin (mg/m^2), mean (SD)	555.9±54.4	578±43.8	0.230[a]
Ejection Fraction (%),median (min-max)	60 (41-78)	64 (40-74)	0.071[b]
Body Weight (kg), median (min-max)	58.5 (49-85)	63.5 (47-73)	0.695[b]
Body Mass Index (kg/m^2), mean (SD)	25.6±4.1	25.1±2.3)	<0.001[a]
Systolic blood pressure (mmHg), median (min-max)	135 (90-170)	120 (90.130)	<0.001[b]
Diastolic blood pressure (mmHg), median (min-max)	85 (60-100)	80 (60.80)	<0.001[b]
Total cholesterol (mg/dl), median (min, max)	215.5 (108-386)	168 (103.199)	<0.001[b]
Fasting blood sugar (mg/dl), median (min, max)	98 (77-219)	91.5 (79.116)	0.178[b]
Creatinin (mg/dl), mean (SD)	0.76±0.12	0.77±0.13)	0.732[a]
CrCl (mL/min/1.73m^2), median (min, max)	93.4 (60.5-112.9)	96.5 (63.6. 119)	0.621[b]
Obesity	9 (26.5%)	-	
Smoking	1 (2.9%)	-	
Hypertension	17 (50%)	-	
Diabetes Mellitus	2 (5.9%)	-	
Dyslipidemia	21 (61.8%)	-	

SD: Standard deviation; Min : minimum, Max: Maximum

Table 2
HRV parameter and mechanical dispersion values

Characteristic	Total n=66	Group I n=34	Group II n=32
LF/HF ratio (ms^2), median (min-max)	2.3 (0.47-9.63)	2,7 (0.4-9.6)	1.9 (0.5-7.3)
Mechanical dispersion (msec), mean (SD)	49±11.9	52.2±13.6	45.7±8.8

LF: Low Frequency; HF: High Frequency; SD: Standard deviation; Min: minimum, Max: Maximum

The median of LF/HF ratio in group I and group II was 2.7 ms2 and 1.9 ms2, respectively. The mean mechanical dispersion in group I and group II was 52.2 ms and 45.7 ms, respectively.

The first hypothesis test is carried out by conducting bivariate analysis. The value of the HRV parameter used is the LF/HF ratio which had the best correlation with mechanical dispersion. The data of LF/HF ratio and mechanical dispersion are numerical with non-normal distribution so bivariate analysis was performed using Spearman's rank correlation (Table 3).

The multivariate analysis using linear regression with the backward method involved independent variables which had a significant value (p <0.05) in bivariate analysis towards mechanical dispersion. However, due to the subjects of group I and II being 34 and 32 people, respectively, there were only 3 independent variables that can be analyzed by multivariate analysis. Independent variables for each group were: systolic blood pressure, doxorubicin cumulative dose, and age (Tables 4 and 5).

The linear regression analysis between the LF/HF ratio and mechanical dispersion in group I showed a more significant P value with a higher correlation value compared to group II, but not significantly different.

Table 3
Bivariate Analysis

Variable	Correlation Coefficient (r)	*P value*
Systolic blood pressure[b]	0.576	<0.001*
Diastolic blood pressure[b]	0.532	<0.001*
Hypertension[a]	0.496	<0.001*
LF/HF ratio[b]	0.491	<0.001*
Cumulative dose of doxorubicin[a]	0.390	0.001*
Obesity[a]	0.384	0.001*
Age[a]	0.365	0.001*
Smoking[a]	0.334	0.003*
Fasting blood sugar[b]	0.305	0.006*
Body mass index[a]	0.304	0.006*
Creatinin clearance[b]	-0.279	0.012*
Body Weight[b]	0.261	0.017*
Ejection Fraction[b]	-0.238	0.027*
Total cholesterol[b]	0.174	0.081
Creatinine[a]	0.171	0.085
Dyslipidemia[a]	0.078	0.267
Diabetes mellitus[a]	-0.036	0.386

Dependent variable : mechanical dispersion, Analysis
a. Pearson; b. rank spearman, (*p < 0.05)

Discussion

The characteristic findings in this study showed significant differences in the characteristics of body mass index, systolic blood pressure, diastolic blood pressure, and total cholesterol between the two groups.

The findings in the study were in accordance with the pathomechanism that occurred between an increase in sympathetic nerves and cardiovascular risk factors because the median LF/HF ratio parameters in group I were slightly higher than group II. The LF/HF ratio showed more autonomic balance, namely the balance between the sympathetic and parasympathetic components and the high LF/HF ratio illustrated greater effect of sympathetic activity on the heart than parasympathetic activity. Previous study conducted by Farahet al.2013 showed an increase in the value LF/HF ratio above normal value in obese patients.[8] Other studies conducted by Junior et al. compared HRV values in hypertensive patients before being given therapy and after administration of antihypertensive therapy. The results of this study indicated that the value of the LF/HF ratio increased in hypertensive patients before administration of therapy compared to on antihypertensive treatment.[9] Similarly, in patients who smoke and have total cholesterol values that exceed normal values, there was an increase in LF/HF ratio,[10,11] but it was different in people with diabetes as there was a decrease in LF and the ratio of LF/HF.[12]

Table 4
Linear Regression Analysis in Group I

Variable	Unstandardized Coefficient		Standardized Coefficient	p value	R^2 *(Adjusted)*
	B	Std Error	B		
Constant	-69.529	22.207		0.004	
SBP	0.293	0.091	0.386	0.003	0.640
LF/HF ratio	1.634	0.742	0.272	0.036	(0.590)
Doxorubicin dose	0.079	0.029	0.322	0.011	
Age	0.669	0.246	0.309	0.011	
Constant	41.997	3.417		0.0001	0.299
LF/HF ration	3.288	0.891	0.546	0.001	(0.277)

Dependent variable: Mechanical dispersion,
R^2: Coefficient of determination,
SBP: Systolic blood pressure

Table 5
Linear Regression Analysis in Group II

Variable	Unstandardized Coefficient		Standardized Coefficient	p value	R^2 *(Adjusted)*
	B	Std. Error	**B**		
Constant	-43.223	16.039		0.012	
SBP	0.030	0.094	0.040	0.751	0.633
LF/HF ratio	1.247	0.610	0.248	0.049	(0.579)
Doxorubicin dose	0.119	0.025	0.588	<0.001	
Age	0.283	0.122	0.286	0.028	
Constant	40.747	2.433		0.0001	0.179 (0.152)
LF/HF ration	2.126	0.831	0,.423	0.016	

Dependent variable : Mechanical dispersion
R^2 :Coefficient of determination
SBP: Systolic blood pressure

Previously, Aagaard et al. showed cardiovascular risk factors such as obesity, hypertension, diabetes, and coronary artery disease influenced prolongation of mechanical dispersion, but this study did not explain the effect of each of these cardiovascular risk factors on prolongation of mechanical dispersion values.[13] The findings in this study were in accordance with previous studies, namely the value of mechanical dispersion in group I was more elongated compared to group II.

In this study, the results of the bivariate analysis of the correlation of HRV parameters, namely LF/HF ratio and mechanical dispersion, there were 3 confounding variables namely systolic blood pressure, cumulative dose of doxorubicin, and age. The first variable is systolic blood pressure. Study conducted by Xie et al. showed an increase in the value of the LF/HF ratio and a decrease in the value of HF in patients who had high systolic blood pressure compared to those with normal systolic blood pressure.[14] This was also in accordance with Junior's et al.[9] Study conducted by Aagaard et al. stated that cardiovascular risk factors, such as hypertension, have a value of mechanical dispersion of more than normal values with a limit of normal mechanical dispersion values of 38 msec, but this study did not explain the effect of high systolic blood pressure values on elongation of mechanical dispersion.[13]

In both groups, the cumulative dose of doxorubicin was almost the same, but the cumulative dose of doxorubicin received by group I was slightly lower compared to group II which was 555.9 mg/m2 (group I) and 578 mg/m2 (Group II), respectively. Table 3 showed the cumulative dose of doxorubicin affects the mechanical dispersion between the two groups (r: 0.390, p: 0.001). Von Hoffet al. and Swain et al. showed an increase in left ventricular dysfunction occurring at cumulative dose of>550 mg/m2.[15,16] Kang et al showed that lymphoma patients receiving anthracycline chemotherapy, epirubicin with an average cumulative dose of 254.15±95.29 mg/m2 was associated with prolongation of mechanical dispersion in breast cancer patients who have received the last cycle of chemotherapy compared to conditions before chemotherapy.[17] Cottin et al and Smith et al stated that the effect of cardiotoxicity was lower in populations receiving epirubicin compared to doxorubicin.[18,19] Nousiainen et al showed a statistically significant sympathetic nervous system predominance with measurements of heart rate variability based on the frequency of low frequency (LF), high frequency (HF), and LF/HF ratio in lymphoma cancer patients get a cumulative dose of doxorubicin>400 mg/m2.[20]

The findings of this study indicate the cumulative dose of doxorubicin affects LF/HF ratio and mechanical dispersion in accordance with previous studies conducted by Kang et al and Nousiainen et al. which showed a cumulative dose of>400 mg/m2 would result in hyperactivity of sympathetic nerves and mechanical dispersion.[17,20]

The third factor that affects improved mechanical dispersion is age. The findings from the bivariate analysis showed moderate correlation between age and mechanical dispersion in both groups (r: 0.365, p: 0.001). This finding is in accordance with a previous study conducted by Rodrigue et al,which stated that the addition of age above 50 years would affect the value of mechanical dispersion.[21]

In group I, the regression analysis using the backward method showed a meaningful moderate correlation between the LF/HF ratio and mechanical dispersion (r: 0.546, p: 0.001). In group II, showed a meaningful moderate correlation between the LF/HF ratio and mechanical dispersion (r: 0.423 p: 0.016) after adjusting the confounding variables.

This study is also the first study to compare the correlation between HRV and mechanical dispersion in post-chemotherapy breast cancer patients after 6 cycles between those with and without cardiovascular risk factors. This study showed a stronger and more significant correlation in group I (r = 0.546, p = 0.001) compared to group II (r = 0.423, p = 0.016), but this difference was not statistically significant. The findings of this study show that cardiovascular risk factors influenced the correlation between HRV and mechanical dispersion. The results of this study are in accordance with previous studies conducted by (1) Farah et al.,8 (2) Junior et al.,9 (3) Ribeiro et al.,12(4) Barutcu et al.,11 (5) Badea et al.,10 and (6) Aagaard et al.13 which stated that cardiovascular risk factors affected the state of hyperactivity of sympathetic nerves and mechanical dispersion, but these six studies did not explain how much influence each cardiovascular risk factor had on changes in HRV values and prolongation of mechanical dispersion values.

Conclusion

There is a difference in the correlation coefficient of heart rate variability with mechanical dispersion in breast cancer patients post anthracycline chemotherapy between those with and without cardiovascular risk factors after anthracycline chemotherapy administration.

There are several cardiovascular risk factors that influenced the prolongation of mechanical dispersion values, including: Hypertension, obesity, smoking, decreased creatinine clearance.

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