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Research Article

Correlation Between Heart Rate and Left Ventricular Ejection Fraction in Peripartum Cardiomyopathy Patients at RSUP Dr. M. Djamil Padang

Nadiva Kezia Sinai[1], Rita Hamdani[2], Andani Eka Putra[3], Eka Fithra Elfi[2], Nelmi Silvia[4], Roza Sriyanti[5]

[1] *Medical Doctor Profession Program, Faculty of Medicine, Universitas Andalas, Padang, 25163, Indonesia*
[2] *Department of Cardiology and Vascular Medicine, Andalas University, RSUP Dr. M. Djamil, Padang, Indonesia*
[3] *Department of Microbiology, Faculty of Medicine, Andalas University, Padang, Indonesia*
[4] *Department of Public Health and Community Medicine, Faculty of Medicine, Andalas University, Padang, Indonesia*
[5] Department of Obstetrics and Gynecology, Faculty of Medicine, Andalas University, RSUP Dr. M. Djamil, Padang, Indonesia

A B S T R A C T

Abstrak

Latar belakang: Peripartum kardiomiopati (PPCM) merupakan salah satu penyebab kematian tertinggi pada ibu hamil setelah melahirkan yang dapat dicegah. Fraksi ejeksi ventrikel kiri menggambarkan derajat kerusakan fungsi sistolik miokardium. Frekuensi denyut jantung mungkin saja dapat digunakan sebagai salah satu indikator prognosis PPCM.

Objektif: Tujuan penelitian ini adalah untuk mengetahui hubungan denyut jantung dan fraksi ejeksi ventrikel kiri saat diagnosis dengan fraksi ejeksi ventrikel kiri setelah 6 bulan pada pasien PPCM.

Metode: Penelitian ini merupakan studi analitik retrospektif observasional. Sampel berasal dari data sekunder yang diperoleh melalui rekam medis pasien PPCM di RSUP Dr. M. Djamil Padang periode 2017-2021, dikumpulkan dengan teknik total sampling, diperoleh 17 sampel yang memenuhi kriteria inklusi. Analisis data dilakukan dengan menggunakan metode regresi logistik sederhana.

Hasil: Hasilnya menunjukkan median usia pasien adalah 32 tahun. Rata-rata indeks massa tubuh adalah 26,32 kg/m2, dengan hipertensi pada kehamilan (58,8%), dengan multiparitas (52,9%), persalinan dengan operasi caesar (88,2%), diagnosis ditegakkan pasca melahirkan (70,6%), terapi dengan ACEi/ARB, beta blocker, spirinolakton (100%); Kategori LVEF 20 – 35% (52.9%), delta LVEF lebih dari 10% setelah 6 bulan (70.59%). Terdapat hubungan yang signifikan secara statistik antara frekuensi denyut jantung 111 - 120 denyut per menit saat diagnosis dan LVEF setelah 6 bulan (p <0,1).

Kesimpulan: Tidak ada hubungan antara frekuensi detak jantung dan LVEF saat diagnosis. Terdapat hubungan antara frekuensi denyut jantung 111 – 120 denyut per menit saat diagnosis dengan LVEF setelah 6 bulan.

Kata kunci: Kardiomiopati peripartum, frekuensi denyut jantung, fraksi ejeksi ventrikel kiri

Abstract

Background: *Peripartum cardiomyopathy (PPCM) is one of the highest preventable causes of death in pregnant women after delivery. Left ventricular ejection fraction (LVEF) describes the degree of damage to myocardial systolic function. Heart rate frequency might be used as one of the prognosis indicators of peripartum cardiomyopathy.*

Objective: *This study aimed to determine the correlation between heart rate frequency at the time of diagnosis and LVEF at the time of diagnosis and after six months in patients with PPCM at Dr. M. Djamil Padang Hospital for 2017-2021.*

Methods: *This is an observational retrospective analytic study. Samples came from secondary data obtained through the medical records of patients with PPCM at Dr. M. Djamil Padang Hospital for 2017-2021. The data were collected using the total sampling technique, and 17 samples met the inclusion criteria. Data analysis was performed using a simple logistic regression method.*

Results: *The results showed the median age of the patients was 32 years. The average body mass index was 26.32 kg/m2, with hypertension in pregnancy (58.8%), with multiparity (52.9%), delivery by cesarean section (88.2%), diagnosis made postpartum (70.6%), therapy with ACEi/ARB, beta blocker, spironolactone (100%); LVEF category 20 – 35% (52.9%), delta LVEF more than 10% after six months (70.59%). There was a statistically significant association between heart rate frequency of 111 - 120 beats per minute at the time of diagnosis and LVEF after six months (p < 0.1).*

Conclusion: *There was no association between heart rate frequency and LVEF at diagnosis. There was an association between heart rate frequency of 111 - 120 beats per minute at diagnosis and LVEF after six months.*

Keywords: *Peripartum cardiomyopathy, heart rate, left ventricular ejection fraction*

What is already known?

The correlation between heart rate frequency at the time of diagnosis and LVEF at the time of diagnosis and after six months in patients with PPCM.

What does this study add?

Characteristics of peripartum cardiomyopathy patients at RSUP Dr. M. Djamil Padang.

CORRESPONDING AUTHOR

Phone: +62-857-5050-6262
E-mail: nadivakezias@gmail.com

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Introduction

Complications in pregnancy remain a major contributor to mortality in women worldwide.[1] The maternal mortality rate in Indonesia continues to increase from 2018 to 7,389 maternal deaths in 2021. Deaths related to hypertension amounted to 1,077 cases, and 335 cardiovascular-related deaths were recorded.[2] In West Sumatra, 183 maternal deaths were recorded in 2021.[3] In fact, two-thirds of the etiology of death in pregnant women is preventable.[4] Cardiomyopathy is the main trigger of death in pregnant women within 42 days to 1 year after termination of pregnancy.[5]

Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy with manifestations of heart failure due to left ventricular systolic dysfunction, with a Left Ventricle Ejection Fraction (LVEF) <45% that appears in late pregnancy or several months after delivery, and there is no previous history of heart disease or other causes of heart failure.[6]

The incidence of PPCM worldwide varies, ranging from 1:300 live births in Haiti to 1:968 in the United States.[7,8] Research at Harapan Kita National Heart Center Hospital from 2010 to 2014 found 49 cases with an average patient age of 30 - 34 years, classified as class III and IV of the NYHA functional classification, with comorbidities of hypertension, anemia, pre-eclampsia, and diabetes mellitus.[9]

Risk factors for PPCM include age, pregnancy-related hypertension, multiparity, multiple gestation, obesity, prolonged use of tocolytics, and black race.[10,11] Clinical manifestations in patients with PPCM often resemble normal pregnancy and peripartum conditions.[12] The primary clinical manifestation of the disease is a decrease in LVEF <45%.[13] and then periodically re-examined LVEF to determine whether there is improvement in the patient's systolic phase.[14]

One of the routine examinations in pregnant women is an examination of vital signs, including checking heart rate.[15] Research conducted by Biswas et al. found that the average heart rate in cardiomyopathy patients was significantly higher.[16] Research conducted by Ryan Cooney et al. in 2022 showed that sinus tachycardia in PPCM patients at the time of diagnosis, the value of the patient's LVEF at the time of diagnosis and after six months would be lower and had a risk of decreasing the LVEF per to <25%.[17] A study conducted by Hoevelmann et al. in 2019 found that sinus tachycardia put patients at a higher risk of death and hospitalization within one year after diagnosis.[18]

Research on PPCM is still very limited in Dr. M. Djamil Hospital Padang. Heart rate can be used as one of the early indicators for the prognosis of PPCM patients assessed based on the results of the LVEF examination.[18] Therefore, the research team is interested in knowing whether there is a relationship between heart rate and LVEF in PPCM patients at Dr. M. Djamil Hospital Padang.

Methods

This study was an observational retrospective analytic study. The population in this study were all patients diagnosed with PPCM in the medical record data of Dr. M. Djamil Padang Hospital in the 2017-2021 period. The minimum sample size in this study was obtained using the unpaired categorical analytic formula, which amounted to 17 samples. The sample was taken using the total sampling technique of PPCM patients that contained data on age, body mass index, hypertension in pregnancy, parity, method of delivery, time of diagnosis, therapy, heart rate frequency at the time of diagnosis, LVEF at the time of diagnosis and six months after. In-depth heart rate was classified based on results from Cooney et al. to retrieve the relationship between specific heart rates and LVEF.

Univariate data on the characteristics of PPCM patients were analyzed. Bivariate data were analyzed between the dependent variable (LVEF) and the independent variable (heart rate) using simple logistic regression analysis and a 90% confidence level.

This study has passed ethical clearance from the Health Research Ethics Commission of Dr. M.

Djamil Hospital Padang with letter number LB.02.02/5.7/204/2023.

Results

Based on the results carried out in February – July 2023, 17 samples met the inclusion criteria.

Table 1. Frequency Distribution of Basic Characteristics of PPCM Patients at Dr. M. Djamil Padang Hospital for the Period 2017 - 2021

Variable		
Age, median (range)	32	19 – 42
BMI (kg/m2), mean (SD)	26.3	3.6
Pregnancy hypertension, n (%)	2	11.8
Preeclampsia/eclampsia	8	47.1
Multiparity	9	52.9
Cesarean section	15	88.2
Diagnosis made in postpartum	12	70.6
Therapy, n (%)		
ACEi/ARB	17	100
Beta-blocker	17	100
Spironolactone	17	100
Diuretic	15	88.2
Bromocriptine	12	70.6
LVEF Classification, n (%)		
36 - 45%	8	47.1
20 - 35%	9	52.9
<20%	0	0
Delta Ejection Fraction		
<5%	0	0
5 – 10%	5	29.4
>10%	2	70.6

Based on Table 1, the median age was 32 years, mean BMI was 26.3 kg/m^2. Hypertension in pregnancy was found in 11.8% of samples, preeclampsia or eclampsia in 47.1% of samples, 52.9% of patients were multiparous, section cesarean delivery in 88.2% of patients, 70.6% of the diagnosis of peripartum cardiomyopathy was done during postpartum. ACEi/ARB, beta blocker, and spironolactone therapy were used in 100% of patients, diuretics in 88.2% of patients, and bromocriptine was given in 70.6% of patients. 52.9% of patients fell into the LVEF category of 20-35%, while 47.1% fell into the 36-45% category. After six months, the LVEF in 29.4% of patients had increased by 1 - 10%, while 70.6% had an improvement in LVEF >10%.

Table 2. Analysis of the Relationship between Heart Rate Frequency at The Time of Diagnosis and LVEF at the time of diagnosis in PPCM Patients at Dr. M. Djamil Padang Hospital in 2017 – 2021

Variable	LVEF at The Time of Diagnosis				P Value
	≥35%		<35%		
	n	Percentage (%)	n	Percentage (%)	
Heart Rate					
<100	2	100	0	0	Reference
100 – 110	3	50	3	50	0.999
111 – 120	3	60	2	40	0.437
>120	1	25	3	75	0.307
Total	9	53	8	47	

Table 2 shows the results of the simple logistic regression statistical test conducted. It showed no statistically significant relationship between heart rate frequency and LVEF at the time of diagnosis in patients with PPCM at Dr. M. Djamil Padang Hospital for 2017-2021 because the p-value was greater than 0.1.

Table 3. Analysis of the Relationship between Heart Rate at the time of diagnosis and LVEF after six months in PPCM Patients at Dr. M. Djamil Padang Hospital 2017 – 2021

Variable	LVEF after 6 Months				P Value
	≥35%		<35%		
	n	%	n	Percentage (%)	
Heart Rate at the time of diagnosis					
<100	1	50	1	50	Reference
100 – 110	5	83.3	1	16.7	0.547
111 – 120	3	60	2	40	0.089
>120	1	25	3	75	0.307
Total	10	58.8	7	41.2	

Table 3 shows the results of the simple logistic regression statistical test conducted, which revealed the statistically significant relationship between heart rate frequency 111 - 120 times per minute at the time of diagnosis and LVEF after six months in patients with PPCM at Dr. M. Djamil Padang Hospital for the period 2017 - 2021 with a p-value of 0.089 ($p < 0.1$).

Discussion

Frequency Distribution of Basic Characteristics of PPCM Patients at Dr. M. Djamil Padang Hospital for the Period 2017 - 2021

The patients have a median age of 32 years, ranging from 19 - 42 years. Similar results were found by Munirwan et al, with an average age of 30 - 34 years.[9] A study at Dr. Soetomo Hospital, Surabaya, found that 60% of cases occurred in patients aged 30 - 39.[19] It was found that estrogen

levels decrease with age, increasing the risk of cardiovascular disease.[2] In addition, old age also increases the likelihood of multiparity, hypertension, and dyslipidemia, which are thought to be risk factors for PPCM.[8]

Based on body mass index, the average patient was classified as overweight, with a value of 26.[3] kg/m[2]. Similar results were obtained by Putra et al. in 2022, which showed a significant association (OR = 1.79) between obesity and the incidence of PPCM.[20] Hemodynamic changes in obesity cause changes in heart structure. Excess adipose tissue increases the thickness of the left ventricle, leads to a larger shock volume, and can cause ventricular dilatation over time.[21] The increase in adipokines by adipose tissue leads to the formation of pro-inflammatory conditions that can precipitate cardiovascular disease.[22]

Patients with hypertension in pregnancy were 11.8%, and preeclampsia or eclampsia were reported in 47.1% of the sample. Research by Bello et al. in 2016 reported hypertension occurred in 37% of patients and eclampsia in 22% of patients. The study also found that the incidence of hypertension in pregnancy was 1.5 times higher, while preeclampsia was 4 times higher in patients with PPCM.[11] Behrens et al., in 2019, also found that the risk of peripartum cardiomyopathy in women with hypertension in pregnancy was 5 - 21 times higher.[23] This may be due to an increase in anti-angiogenic factors, such as the SFlt-1 gene related to the pathophysiology of hypertension in pregnancy and PPCM. Hemodynamic changes due to hypertension in pregnancy also increase cardiac stress during pregnancy. It was found that in 80% of preeclamptic women, there are compensatory changes in the myocardium, and 50% of preeclamptic women have ventricular dysfunction.[24]

In this study, there were 52.9% of patients with multiparity. This is in line with Wu et al. in 2017, which showed multiparity as a significant risk factor in the occurrence of PPCM.[25] Bello et al. showed 67% of cases of PPCM in women with multiparity.[11] Repeated pregnancies may cause a shift in blood pressure regulation due to continuous changes in vascular compliances and endothelium-dependent vasoconstriction.[26] In addition, women with grand multiparity had a higher BMI compared to other parity groups.[22]

This study showed that 88.2% of patients underwent cesarean section delivery. Studies conducted by Wu et al. and Lee et al. showed that 66.1% and 64.5% of patients were undergoing cesarean section, respectively.[25,27] Caesarian delivery is mainly performed in PPCM patients with complications that require immediate delivery.[27] A critical focus of PPCM therapy is to reduce preload and afterload. Sectio-caesarean delivery can reduce the risk of increased stroke volume and cardiac output. With immediate termination of pregnancy, the patient's hemodynamic stability is expected to be better maintained.[28]

70.6% of the diagnosis in this study was made during postpartum. This is in line with the studies of Hoevelmann et al. and Wu et al., which respectively showed 82.4% and 90% of postpartum diagnoses.[25,29] This may occur because the symptoms of the disease resemble the physiological conditions of pregnant women. Some patients do not show symptoms until after delivery. In addition, PPCM is a diagnosis of exclusion without a specific examination as the gold standard, so it takes longer to establish this diagnosis.[12]

The most used therapies in this study were ACEi/ARB, beta blocker, and spironolactone in 100% of patients, diuretics in 88.2% of patients, and bromocriptine in 70.6% of patients. A meta-analysis study by Hoevelmann et al. in 2022 showed similar results, with the most common order of therapy starting with diuretics, ACEi/ARBs, beta-blockers, and bromocriptine. The main goals of PPCM therapy include five things, namely, optimization of preload and oxygenation, hemodynamic stabilization, immediate delivery, and the use of adjuvant therapy.[30]

This study showed that 52.9% of patients belonged to the LVEF category of 20-35%, 47.1% fell into the 36-45% category, and no patients with LVEF <20%. Hoevelmann et al.'s meta-analysis study in 2022 showed an average LVEF of 29.1%. Achmad et al. showed that the average LVEF of patients was 32.34 ± 6.3%.[29,31] A decrease in LVEF in patients with PPCM can occur because the weakened heart muscle cannot contract effectively. In some cases, left ventricular dilation also occurs.[32]

Changes in LVEF after six months in this study showed 70.6% had an increase in LVEF of more than 10%, and 29.4% of patients increased by 5 - 10%. Similar results were found by Hoevelmann et al., who showed that after six months, the average

patient had an improvement in ejection fraction worth 17.7%.[29] Peripartum cardiomyopathy patients are said to have a complete cure if the LVEF value is ≥55% or is in class I on the NYHA functional classification.[33] The varying cure rates of PPCM worldwide are greatly influenced by access to health facilities, better intensive care, and affordability of the latest heart failure therapies.[33]

Analysis of the Relationship between Heart Rate Frequency at the time of diagnosis and LVEF at The Time of Diagnosis in PPCM Patients at Dr. M. Djamil Padang Hospital 2017 - 2021 Period

The results of statistical tests using the simple logistic regression method conducted on the analysis of the relationship between heart rate frequency at the time of diagnosis and LVEF at the time of diagnosis in patients with PPCM at Dr. M. Djamil Padang Hospital for the period 2017 - 2021 showed a p-value of more than 0.1, indicating that there was no statistically significant relationship.

This finding differs from a study by Cooney et al. in 2022, which found sinus tachycardia was significantly associated with lower LVEF values at the time of diagnosis.[17] Meanwhile, Hoevelmann et al., in 2019 found tachycardia in 31.8% of patients, with a median LVEF value of 33%, and almost 2 out of 3 patients had LVEF results ≤35%.[18] The difference in research results can be caused by differences in demographic distribution, where the Cooney and Hoevelmann studies showed 25% and 53.5% of patients were black, respectively.[17,18] Studies show that blacks have a higher prevalence, diagnosed at a younger age, more often have a previous history of hypertension, and worse outcomes. In addition, there are differences in cardiac remodeling in response to cardiac stressors between black and white populations. These differences may be related to genetic variations or variations in the pathophysiologic pathways of the disease.[30]

A study by Ricci et al. found that a progressive decrease in ejection fraction with increasing heart rate would only occur if the increase were more than 30 beats per minute compared to the physiological heart rate range.[34] Another study by Nanchen et al. on Resting Heart Rate and the Risk of Heart Failure in Healthy Adults suggested that heart rate frequency independently cannot replace markers of heart failure and can still intersect with several confounding factors. For example, circadian variations in heart rate are related to neurohormonal factors and a person's physical activity. This causes the measurement results to differ depending on the time of measurement.[35]

In addition, the heart rate examination obtained in this study may have been performed when the patient was experiencing a change in posture, where there can be an increase in heart rate of 30 - 35%. Examinations performed when the patient is experiencing increased physical activity can also gradually increase heart rate frequency, which is influenced by the autonomic nervous system. Other variables that can affect heart rate include age, race, blood pressure, medication use, mental state, lifestyle, smoking, and alcohol consumption.[36]

Analysis of the Relationship between Heart Rate Frequency at The Time of Diagnosis and LVEF after Six Months in PPCM Patients at Dr. M. Djamil Padang Hospital 2017 - 2021 Period

The results of statistical tests using the simple logistic regression method show that there is a statistically significant relationship between heart rate frequency of 111 - 120 beats per minute at the time of diagnosis and LVEF after six months in patients with PPCM at Dr. M. Djamil Padang Hospital for the period 2017 - 2021 with a p-value of 0.089 ($p < 0.1$).

Research conducted by Cooney et al. in 2022 stated that sinus tachycardia at the time of diagnosis was statistically significantly associated with recovery after six months. Patients with a heart rate frequency of more than 100 beats per minute were 63% less likely to experience improvement in LVEF. In addition, a heart rate frequency of more than 110 beats per minute was associated with a five times higher mortality rate.[17] A 2019 study by Hoevelmann et al. found 27.9% of patients had a poor outcome after six months. This percentage was found in patients with a significantly higher heart rate frequency. The study explained that sinus tachycardia was associated with an increased risk of death or re-hospitalization in the six months and 12 months after diagnosis.[18]

Sinus tachycardia is an exaggerated sympathetic autonomic nervous system response to advanced heart failure. A significant reduction in heart rate between the patient's initial and subsequent visits is associated with left ventricular recovery and response to appropriate

management of PPCM. This is further supported by studies showing that there is potential clinical benefit in heart failure repair using ivabradine with the therapeutic goal of reducing heart rate frequency as ivabradine binds to I_f channel in sinoatrial (pacemaker) nodal cells and disrupts the flow of sodium and potassium.[30,37]

The increased heart rate frequency that occurs in patients with cardiomyopathy may increase the likelihood of myocardial ischemia, arrhythmias, and ventricular dysfunction. High heart rate frequency may also mediate pro-inflammatory activation. This may cause endothelial dysfunction through decreased expression of endothelial nitric oxide synthase (eNOS) and increased secretion of cytokines and pro-thrombotic molecules.[32]

However, various factors have been reported to affect the recovery rate of PPCM patients, such as age, blood pressure, NYHA functional classification, LVEF, and others. Thus, once a diagnosis of PPCM is made in a patient, risk stratification involving various parameters should be done immediately to increase awareness of the possibility of unwanted complications.[30]

As the incidence of PPCM is still relatively rare, the sample size for this study was limited, which affected the limitations of the analysis and interpretation of the study. The heart rate frequency data obtained in this study was not conducted simultaneously and under similar conditions in each patient, which may affect the bias in the measurement. Furthermore, most of the stabilized PPCM patients had been referred back to their respective health facilities, so data on their condition after six months could not be traced further. In addition, this study only focused on the effect of heart rate frequency from many variables that can affect the LVEF of PPCM patients.

Conclusion

In this study, it was found that there was no statistically significant relationship between heart rate frequency and LVEF at the time of diagnosis in patients with PPCM at Dr. M. Djamil Padang Hospital 2017-2021 period, and there was a statistically significant relationship between heart rate frequency 111-120 times per minute at the time of diagnosis and LVEF after six months in patients with PPCM at Dr. M. Djamil Padang Hospital 2017-2021 period.

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