Heart Rate Variability Analysis to Investigate Autonomic Nervous System Activity among the Three Premature Ventricular Complex Circadian Types: An Observational Study

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ABSTRACT

Background and Objective. Premature ventricular complex (PVC) burden exhibits one of three circadian types, classified as fast-type, slow-type, and independent-type PVC. It is unknown whether PVC circadian types have different heart rate variability (HRV) parameter values. Therefore, this study aimed to evaluate differences in HRV circadian rhythm among fast-, slow-, and independent-type PVC.

Methods. This cross-sectional observational study consecutively recruited 65 idiopathic PVC subjects (23 fast-, 20 slow-, and 22 independent-type) as well as five control subjects. Each subject underwent a 24-hour Holter to examine PVC burden and HRV. HRV analysis included components that primarily reflect global, parasympathetic, and sympathetic activities. Repeated measures analysis of variance was used to compare differences in HRV circadian rhythm by PVC type.

Results. The average PVC burden was 15.7%, 8.4%, and 13.6% in fast-, slow-, and independent-type idiopathic PVC subjects, respectively. Global, parasympathetic nervous system, and sympathetic nervous system HRV parameters were significantly lower in independent-type PVC versus fast- and slow-type PVC throughout the day and night. Furthermore, we unexpectedly found that tendency towards sympathetic activity dominance during nighttime was only in independent-type PVC.

Conclusion. The HRV parameters are reduced in patients with independent-type PVC compared to fast- and slow-type PVC. Future research is warranted to determine possible differences in the prognosis between the three PVC types.

Keywords: premature ventricular complex, circadian rhythm, autonomic nervous system, heart rate variability

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INTRODUCTION

Idiopathic premature ventricular complex (PVC) is the most common type of ventricular arrhythmia with a prevalence of 5–12%.[1] Of all idiopathic PVC patients, 88% of patients had a high burden of PVC.[2] Patients with PVC burden equals to or more than 5% for 24 hours have increased risk of lower left ventricular ejection fraction.[3] Moreover, the constant PVC burden throughout the day and night even increases the risk of cardiomyopathy.[4]

Recent data shows that there are three PVC burden circadian patterns, classified as fast-type (48% of cases), slow-type (16% of cases), and independent-type (36% of cases).[5] In fast-type, the PVC burden is positively correlated with heart rate. Fast-type PVC burden increases as the heart rate increases which leads to high PVC burden during daytime and low PVC burden during nighttime. Conversely in slow-type, the PVC burden is negatively correlated with heart rate. Slow-type PVC burden increases as the heart rate decreases, hence PVC burden rises overnight to early morning. In independent-type, the PVC burden stays consistent throughout day and night irrespectively of increase or decrease in heart rate.[6]

The cardiac circadian rhythm is regulated or modulated by autonomic nervous system (ANS). Heart rate variability (HRV) is an established non-invasive method for the assessment of ANS activity.[7] HRV is the change in the R-R beat-to-beat interval, which is related to the interaction between the sympathetic nervous system and the parasympathetic nervous system.[7,8] Several studies have shown that lower HRV was associated with higher cardiovascular events and mortality whereas high HRV showed higher cardiac fitness.[9,10] Previous studies have found that ANS activity fluctuates during the 24-h period like a biological clock, or exhibits a circadian pattern.[11,12] For instance, Ma et al.[12] reported mean HRV are different at different times of the day, particularly the day-night differences. However, the literature remains restricted in relation to studies that evaluate the HRV among PVC circadian types. Therefore, the aim of this study was to analyze and compare the HRV rhythm in PVC patients according to circadian types, namely, fast, slow-, and independent-type PVC. We hypothesized that there would be different HRV circadian rhythm between fast, slow-, and independent-type PVC.

METHODS

Study Design and Ethical Aspects

This was a cross-sectional observational study exploring the differences of HRV circadian rhythm among three PVC circadian types. The institutional review board of National Cardiovascular Center Harapan Kita, Indonesia approved this study (IRB number: UM.01.05/2.2.2/209/2022). All subjects provided written informed consent prior to participation.

Study Subjects

This study was performed at the outpatient clinic of the National Cardiovascular Center Harapan Kita, Pakuhaji Hospital, and Bun Hospital, Indonesia. Samples were collected consecutively from July 2022 to December 2022. Symptomatic patients with PVC burden equal to or greater than 5% per day during 24-hour Holter recording were identified and the circadian rhythm pattern was then determined as fast-type, slow-type, or independent-type PVC. If PVC burden was positively correlated with heart rate (Pearson's correlation coefficient ≥0.3 with $p < 0.05$), then the patient was classified as fast-type PVC. If PVC burden was negatively correlated with heart rate (Pearson's correlation coefficient ≤ -0.3 with $p < 0.05$), then the patient was classified as slow-type PVC. If there is no relationship between PVC burden and heart rate (the Pearson's correlation coefficient -0.3 to +0.3), then the patient was classified as independent-type PVC.[13]

Clinical data of each subject were collected from medical interviews and questionnaires. For subjects who cannot be contacted at the first try, we tried again the next week to contact to minimize selection bias. Demographic and anthropometric characteristics included age, gender, body mass index (BMI), previous medical history, and current medication usage. Patients with any form of structural heart disease (ejection fraction below 50% or regional wall motion abnormalities on echocardiographic examination, moderate to severe heart valve disorders, and congenital heart disease), multifocal PVCs, atrial fibrillation, pulmonary hypertension, impaired liver or renal function, electrolyte abnormalities were excluded from the study. From the sample size calculation for independent groups, the number of samples required was 18 samples for each group. In addition, five healthy adults who were matched for age and gender with the three PVC groups, were enrolled as controls. The number of controls in this study was five considering that a control group was needed as a benchmark for research results, but they were not included in statistical analysis. These controls were recruited from well-patient visits in the clinic.

Procedure

Twelve-lead electrocardiography (ECG) was performed to evaluate the evidence of PVC, and 24h Holter monitoring was performed in all included participants. All participants adhered to a routine of diurnal activity and nighttime sleep. In patients who were already prescribed with beta-blockers, we performed Holter recording after stopping the drug for three days; and patients who were prescribed anti-arrhythmic drugs were excluded. Holter arrhythmia analysis was performed with computer-assisted software (Bold Technologies Leading Cardiopoint) and then visually rechecked. PVC burden was calculated and HRV was analyzed at each of three time points: morning (02:00–09:59), day (10:00–17:59), and night (18:00–01:59). Holter results with time frames containing >10% signal loss were excluded from the analysis.

PVC burden was defined as the percentage of PVC of total ventricular beats (% of the number of PVC/the number of total beats). The time- and frequency-domain HRV parameters were calculated with the software:[14,15] standard deviation of normal R-R intervals (SDNN), standard deviation of the average normal-to-normal (NN) intervals calculated over 5-minute intervals (SDANN), root mean square of successive R-R interval differences (RMSSD), and percentage of normal R-R intervals that differ by 50 ms (PNN50), high frequency (HF) power, low frequency (LF) power, and LF/HF ratio. SDNN and SDANN represent overall autonomic nervous system activity. RMSSD, PNN50, and HF represent parasympathetic nervous system activity. LF represents sympathetic nervous system activity. LF:HF ratio represents balance between sympathetic nervous system and parasympathetic nervous system activity.

Statistical Analysis

Quantitative baseline characteristics data were presented as mean ± SD and compared among fast-, slow-, and independent-type groups using one-way analysis of variance (ANOVA). Categorical data were expressed as number and compared among groups using chi-squared tests. Repeated measures ANOVA was used to test differences in circadian rhythm of all HRV parameters between fast-, slow-, independent-type PVC subjects. Hypertension has previously been observed as one of prevalent comorbidities in PVC patients[16], and since hypertension proportion was not equally distributed among groups, analysis of covariance (ANCOVA) including hypertension as covariate was performed. In case of significant group differences, a Games-Howell post-hoc test was applied to test between-group differences. Data from the control subjects as the benchmark references were included in table and figures, but they were not included in statistical analysis. We included analyses only to samples with complete data on heart rate variability. Data analysis was performed using statistical package for the social sciences (SPSS) software version 23.

RESULTS

A total of 147 patients were consecutively evaluated. Forty-seven patients did not meet the required inclusion criteria. From the remaining 100 patients, 65 patients agreed to participate and all of them were finally included in the present study. A total of 23 fast-type (mean PVC burden ± SD=15.7% ± 7.1), 20 slow-type (8.5% ± 2.4), and 22 independent-type (13.6% ± 5.1) PVC subjects were included in this study. Fast-type PVC subjects were older than independent- and slow-type PVC subjects, but this difference was not statistically significant (Table 1). Independent-type PVC had a significant smaller proportion of hypertension compared to fast- and slow-type PVC.

Heart rate and PVC burden circadian rhythm are presented in Figure 1. Heart rate in independent-type PVC was higher than fast- and slow-type PVC. The gap is clear between heart rate of independent-type PVC and fast- or slow-type PVC, especially at night. Even so, the three groups had similar pattern of heart rate circadian rhythms, which was higher in the morning and lower at night.

In Figures 2-4, the repeated measures ANOVA showed that there were significant differences in circadian rhythms of global HRV, parasympathetic nervous system activity, and sympathetic nervous system activity between the fast-, slow, and independent-type PVC (p value, respectively: SDNN <0.001; SDANN <0.001; RMSSD <0.001; pNN50 <0.001; HF <0.001; LF 0.011). Hypertension was not statistically significant as covariate in ANCOVA, hence hypertension had no account for the results of HRV parameters' comparisons among groups. Post-hoc analysis showed that either in the morning, during the day, or at night, the overall values of HRV were higher in fast- and slow-type idiopathic PVC

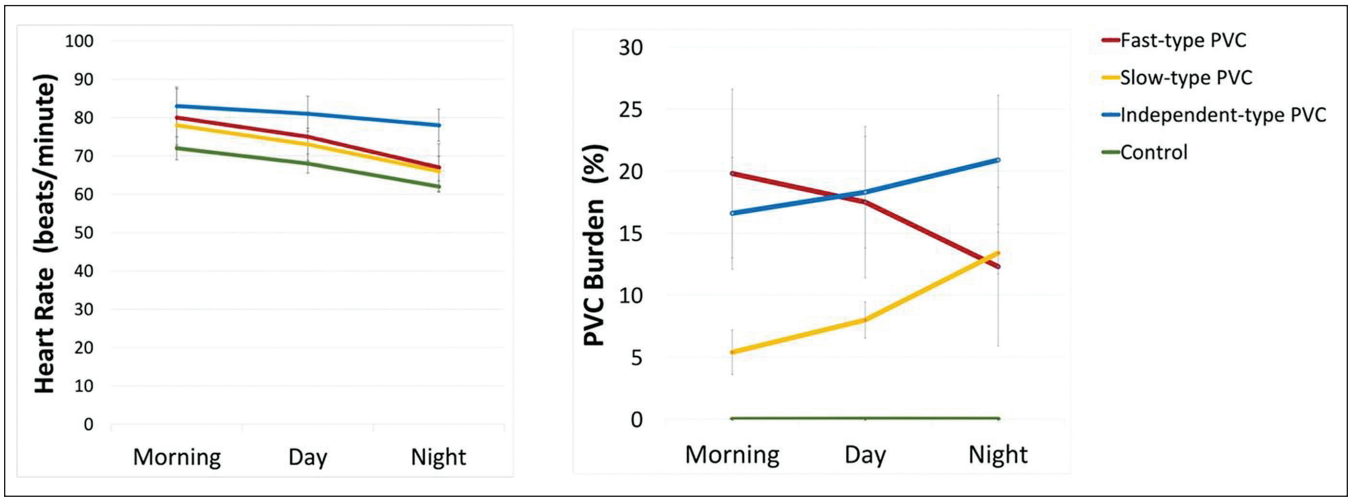


Figure 1. Circadian rhythm of heart rate and PVC burden.[17]

Table 1. Baseline Characteristics of Idiopathic PVC Patients[17]

Characteristic	Fast-type (n=23)	Slow-type (n=20)	Independent-type (n=22)	*p* value	Control (n=5)
Age, years (SD)	51 (12)	44 (13)	45 (13)	0.237[a]	40 (6)
Gender					
Male	4	6	6	0.594[b]	2
Female	19	14	16		3
Marital status					
Never married	2	2	2	0.988[b]	1
Married	21	18	20		4
Education					
Less than high school	16	17	15	0.392[b]	2
High school graduate	7	3	7		3
Employment status					
Unemployed	14	9	11		2
Employed	9	11	11	0.562[b]	3
Alcohol consumption					
No	21	20	22	0.791[b]	5
Occasionally	2	-	-		-
Dyslipidemia					
No	14	13	20	0.053[b]	4
Yes	9	7	2		1
Diabetes					
No	23	20	20	0.777[b]	5
Yes	-	-	2		-
Hypertension					
No	11	6	18	0.002[b]	3
Yes	12	14	4		2
CCB use					
No	20	17	22	0.501[b]	5
Use	3	3	-		-
Beta-blocker use					
No	8	10	9	0.599[b]	3
Yes	15	10	13		2
BMI, kg/m² (SD)	25.6 (4.4)	23.4 (2.4)	24.9 (3.9)	0.167[a]	24 (4.1)

SD = standard deviation; CCB = calcium-channel blocker; BMI = body mass index; a = one-way ANOVA test; b = chi-square test

compared to independent-type idiopathic PVC (p value <0.05). Also, LF/HF ratio circadian rhythm displaying trend towards higher values during nighttime was only in independent-type PVC.

DISCUSSION

One major finding of this study is that in patients with independent-type PVC, the oscillations of HRV have distinct abnormalities. These abnormalities include attenuation of the global, parasympathetic, and sympathetic nervous system HRV parameters throughout day and night. The autonomic nervous system functions in independent-type PVC are less preserved than fast- and slow-type PVC. Another finding is that the tendency towards higher LF/HF ratio at night in independent-type PVC characterizes those with the nighttime sympathetic dominance.

In control subjects, global HRV during the day was higher than in the morning. In addition, the parasympathetic nervous system activity at night was higher than in the morning and daytime. This is consistent with previous studies which stated that the time-domain HRV (RMSSD and pNN50) and HF power increased during sleep.[18] After that, they decreased with the lowest point in the morning. Like many other biomarkers, autonomic nervous system activity physiologically fluctuates in a diurnal variation pattern with peak levels of vagal activity at night. Conversely, a blunted pattern of circadian variation, especially in the absence of increased nocturnal vagal activity is associated with an increased risk of cardiovascular events such as myocardial ischemia, myocardial infarction, malignant arrhythmias, and sudden cardiac death in the morning as well as a hyperglycemic state and elevated pro-inflammatory cytokines.[15]

In fast-and slow-type PVC, the mean SDNN and SDANN were higher than the control group in the morning, day, and night. These SDNN and SDANN variations indicate the flexibility of the autonomic nervous system as an adaptation to day-night variations in PVC burden. Increased SDNN and SDANN were also found in atrial fibrillation patients.[19] Kim et al.[19] suggested that high global HRV in atrial fibrillation might reflect disproportionate fluctuation in the autonomic nervous system. In fast- and slow-type PVC,

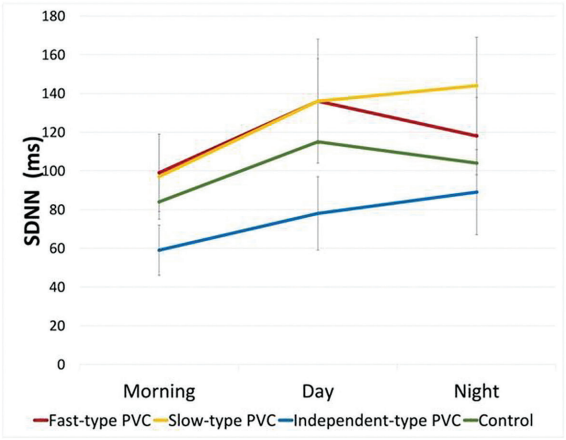
both parasympathetic and sympathetic nervous system tone are higher at night than in the morning and during the day. However, the autonomic nervous system activity in fast- and slow-type PVC was kept at balance as shown by dominance of the parasympathetic nervous system at night compared to the sympathetic nervous system, because there was a decrease in the LF/HF ratio at night compared to morning and daytime.

Subjects of independent-type PVC in this study showed a trend of higher resting heart rate compared to fast- and slow-type PVC, which indicated the high sympathetic drive.[20,21] Patients with PVC were known to have higher sympathetic nervous activity than normal people.[22] However, spectral analysis showed the reduced LF component which characterizes decreased sympathetic tone variability in the heart. One possible reason for the low cardiovascular variability of this component of LF could be due to downregulation of β-adrenoceptors. Prolonged stimulation of β-adrenoceptor signals can induce β-adrenoceptor downregulation. Sympathetic adrenergic activation, mediated via β-adrenoceptor signaling, enhances cardiac contraction and relaxation. This response is initially beneficial in helping to increase cardiac output and maintain circulation. However, long-term β-adrenoceptor overstimulation eventually leads to a loss of responsiveness to sympathetic signaling (β-adrenoceptor desensitization) and a decrease in the density (number) of β-adrenoceptors in the cell membrane (downregulation), resulting in reduced β-adrenoceptor signaling. β-adrenoceptor desensitization occurs via β-adrenoceptor self-phosphorylation by protein kinase A and G-protein coupled receptor kinases (GRKs).[23] GRKs activity has been found to increase under conditions of prolonged β-adrenoceptor activation. In addition, GRK activation can lead to internalization of β-adrenoceptors

(A) Circadian rhythm of SDNN

SDNN (ms)	Fast-type	Slow-type	Independent-type[a,b]	p value	Control
Morning	99 (20)	97 (22)	59 (13)		84 (5)
Day	136 (22)	136 (32)	78 (19)	< 0.001	115 (7)
Night	118 (20)	144 (25)	89 (22)		104 (26)

a= significantly different from fast-type (Games-Howell post-hoc test, p<0.05);
b= significantly different from slow-type (Games-Howell post-hoc test, p<0.05)



(B) Circadian rhythm of SDANN

SDANN (ms)	Fast-type	Slow-type	Independent-type[a,b]	p value	Control
Morning	80 (16)	84 (16)	49 (12)		66 (8)
Day	120 (24)	131 (28)	71 (17)	< 0.001	100 (7)
Night	94 (22)	116 (25)	78 (18)		78 (6)

a= significantly different from fast-type (Games-Howell post-hoc test, p<0.05);
b= significantly different from slow-type (Games-Howell post-hoc test, p<0.05)

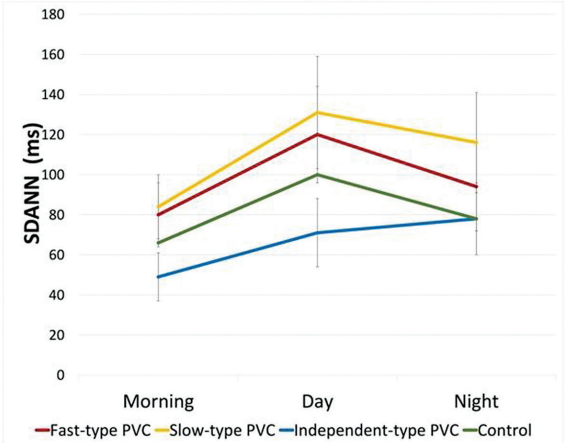


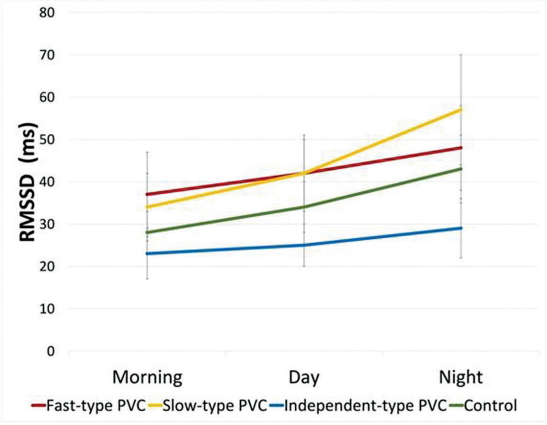
Figure 2. Circadian rhythm of global HRV in idiopathic PVC.

SDNN = standard deviation of normal R-R intervals; SDANN = standard deviation of the averages of NN intervals in all 5-minute segments.

(A) Circadian rhythm of RMSSD

RMSSD (ms)	Fast-type	Slow-type	Independent-type[a,b]	p value	Control
Morning	37 (10)	34 (8)	23 (6)		28 (5)
Day	42 (8)	42 (9)	25 (5)	< 0.001	34 (6)
Night	48 (10)	57 (13)	29 (7)		43 (8)

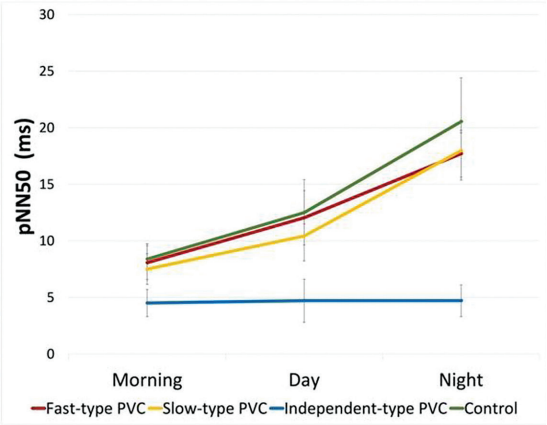
a= significantly different from fast-type (Games-Howell post-hoc test, p<0.05);
b= significantly different from slow-type (Games-Howell post-hoc test, p<0.05)



(B) Circadian rhythm of pNN50

pNN50 (%)	Fast-type	Slow-type	Independent-type[a,b]	p value	Control
Morning	8.06 (1.5)	7.49 (1.36)	4.5 (1.2)		8.38 (1.35)
Day	12.03 (2.4)	10.41 (2.2)	4.7 (1.9)	< 0.001	12.48 (2.91)
Night	17.69 (2.07)	17.96 (2.6)	4.7 (1.4)		20.53 (3.87)

a= significantly different from fast-type (Games-Howell post-hoc test, p<0.05);
b= significantly different from slow-type (Games-Howell post-hoc test, p<0.05)



(C) Circadian rhythm of HF

HF (ms)	Fast-type	Slow-type	Independent-type[a,b]	p value	Control
Morning	0.22 (0.04)	0.22 (0.08)	0.13 (0.08)		0.23 (0.06)
Day	0.27 (0.04)	0.26 (0.10)	0.14 (0.07)	< 0.001	0.24 (0.06)
Night	0.33 (0.09)	0.34 (0.12)	0.14 (0.07)		0.26 (0.08)

a= significantly different from fast-type (Games-Howell post-hoc test, p<0.05);
b= significantly different from slow-type (Games-Howell post-hoc test, p<0.05)

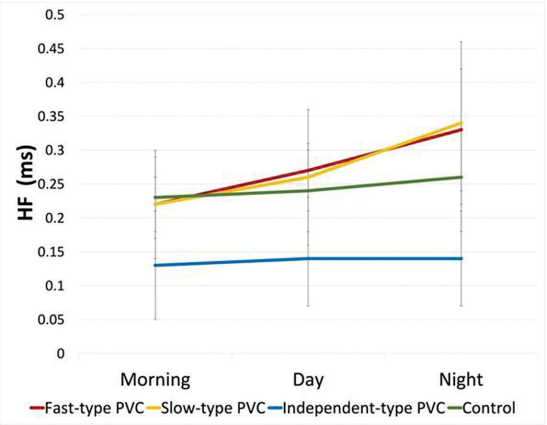


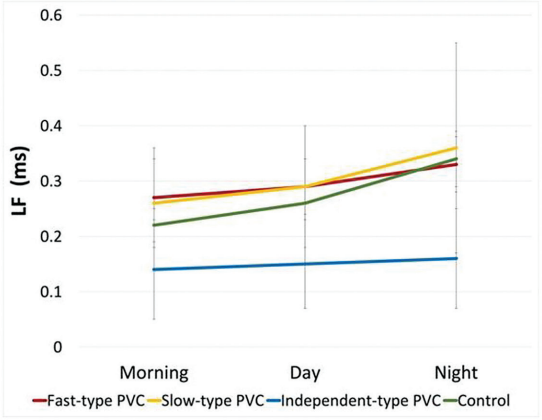
Figure 3. Circadian rhythm of parasympathetic activity in idiopathic PVC.

RMSSD = root mean square of successive R-R interval differences; pNN50 = percentage of normal R-R intervals that differ by 50 ms; HF = high frequency.

(A) Circadian rhythm of LF

LF (ms)	Fast-type	Slow-type	Independent-type[a,b]	p value	Control
Morning	0.27 (0.09)	0.26 (0.08)	0.14 (0.09)		0.22 (0.03)
Day	0.29 (0.05)	0.29 (0.11)	0.15 (0.08)	0.011	0.26 (0.03)
Night	0.33 (0.05)	0.36 (0.19)	0.16 (0.09)		0.34 (0.05)

a= significantly different from fast-type (Games-Howell post-hoc test, p<0.05);
b= significantly different from slow-type (Games-Howell post-hoc test, p<0.05)



(B) Circadian rhythm of LF/HF ratio

LF/HF ratio	Fast-type	Slow-type	Independent-type	p value	Control
Morning	1.27 (0.28)	1.29 (0.22)	1.07 (0.20)		1.14 (0.36)
Day	1.19 (0.25)	1.24 (0.23)	1.12 (0.17)	0.05	1.03 (0.27)
Night	1.08 (0.29)	1.16 (0.30)	1.19 (0.16)		0.84 (0.20)

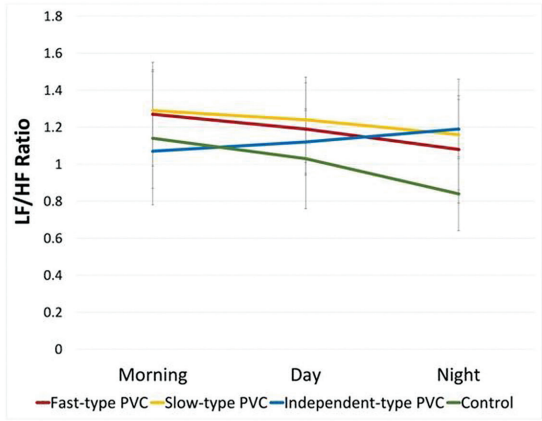


Figure 4. Circadian rhythm of sympathetic activity and sympathovagal balance in idiopathic PVC.
LF = low frequency; HF = high frequency.

(especially β1-adrenoceptors), β1-adrenoceptors shift from the sarcolemma membrane to the cytosolic compartment, contributing to the downregulation of β-adrenoceptors.

In independent-type PVC with its consistency of PVC burden throughout day and night, all physiological mechanisms reached maximum capacity to maintain homeostasis, the autonomic nervous system was unable to keep reserves on its variability. The ability to maintain a high level of variability is a marker of cardiovascular health. Previous studies have shown that lower HRV is associated with a 32–45% increased risk of a first cardiovascular event in patients without known cardiovascular disease.[24] The phasic characteristics of global, sympathetic, and parasympathetic drive are clearly evident in control, fast- and slow-type PVC subjects, but not in patients with independent-type PVC.

This study has limitations in its cross-sectional design. Because this study is observational in nature, there may be residual confounders. We only investigated patients from Jakarta and Tangerang, and generalizing our study findings to represent an entire country should be done with caution. Future studies should invite more centers to participate and a follow-up to evaluate possibility of differences in prognosis.

CONCLUSION

The global, parasympathetic, and sympathetic parameters of HRV are reduced in patients with independent-type PVC compared to fast- and slow-type PVC. In fast- and slow-type PVC, there were slight increases of HRV indicating increased ANS activity as adaptation to the stress imposed by the PVC burden.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

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REFERENCES

1. Marcus GM. Evaluation and management of premature ventricular complexes. Circulation. 2020 Apr 28;141(17):1404-18. doi: 10.1161/CIRCULATIONAHA.119.042434. PMID: 32339046.
2. Asatryan B, Seiler J, Bourquin L, Knecht S, Servatius H, Madaffari A, et al. Pre-procedural arrhythmia burden and the outcome of catheter ablation of idiopathic premature ventricular complexes. Pacing Clin Electrophysiol. 2021 Apr;44(4):703-10. doi: 10.1111/pace.14211. PMID: 33675240.
3. Parreira L, Marinheiro R, Amador P, Mesquita D, Farinha J, Lopes A, et al. Frequent premature ventricular contractions: association of burden and complexity with prognosis according to the presence of structural heart disease. Ann Noninvasive Electrocardiol. 2021 Jan;26(1):e12800. doi: 10.1111/anec.12800. PMID: 32964593; PMCID: PMC7816816.
4. Dabbagh GS, Bogun F. Predictors and therapy of cardiomyopathy caused by frequent ventricular ectopy. Curr Cardiol Rep. 2017 Sep;19(9):80. doi: 10.1007/s11886-017-0887-1. PMID: 28752278.
5. Hamon D, Swid MA, Rajendran PS, Liu A, Boyle NG, Shivkumar K, et al. Premature ventricular contraction diurnal profiles predict distinct clinical characteristics and beta-blocker responses. J Cardiovasc Electrophysiol. 2019 Jun;30(6):836-43. doi: 10.1111/jce.13944. PMID: 30964570.
6. Chen M, Wang Q, Sun J, Zhang P-P, Li W, Zhang R, et al. Utility of circadian variability patterns in differentiating origins of premature ventricular complexes. J Interv Cardiol. 2020 Oct 30;2020:7417912. doi: 10.1155/2020/7417912. PMID: 33177963; PMCID: PMC7647775.
7. Acharya UR, Joseph KP, Kannathal N, Lim CM, Suri JS. Heart rate variability: A review. Med Biol Eng Comput. 2006 Dec;44(12):1031-51. doi: 10.1007/s11517-006-0119-0. PMID: 17111118.
8. Cygankiewicz I, Zareba W. Heart rate variability. First edition. Handbook of Clinical Neurology. London: Elsevier BV; 2013. pp. 379–93.
9. Fang SC, Wu YL, Tsai PS. Heart rate variability and risk of all-cause death and cardiovascular events in patients with cardiovascular disease: a meta-analysis of cohort studies. Biol Res Nurs. 2020 Jan;22(1):45-56. doi: 10.1177/1099800419877442. PMID: 31558032.
10. Hillebrand S, Gast KB, de Mutsert R, Swenne CA, Jukema JW, Middeldorp S, et al. Heart rate variability and first cardiovascular event in populations without known cardiovascular disease: meta-analysis and dose-response meta-regression. Europace. 2013 May;15(5):742-9. doi: 10.1093/europace/eus341. PMID: 23370966.
11. Bonnemeier H, Richardt G, Potratz J, Wiegand UKH, Brandes A, Kluge N, et al. Circadian profile of cardiac autonomic nervous modulation in healthy subjects: differing effects of aging and gender on heart rate variability. J Cardiovasc Electrophysiol. 2003 Aug;14(8):791-9. doi: 10.1046/j.1540-8167.2003.03078.x. PMID: 12890036.
12. Ma Y, Chang MC, Litrownik D, Wayne PM, Yeh GY. Day-night patterns in heart rate variability and complexity: differences with age and cardiopulmonary disease. J Clin Sleep Med. 2023 May 1;19(5):873-82. doi: 10.5664/jcsm.10434. PMID: 36692177; PMCID: PMC10152358.
13. Park YM, Kim CY, Seo J, Jang AY, Cha MS, Kang WC, et al. Significant reduction in the density of premature ventricular complex with ß-blocker medication in fast rate-dependent premature ventricular complex. Int J Arrhythm. 2020;21:1–8. doi: 10.1186/s42444-020-00028-2.
14. Jarczok MN, Guendel H, McGrath JJ, Balint EM. Circadian rhythms of the autonomic nervous system: Scientific implication and practical implementation. In: Svorc P, editor. Chronobiology - The Science of Biological Time Structure [Internet]. London: IntechOpen; 2019 [cited 2023 Jan 5]. Available from: https://www.intechopen.com/chapters/67730.
15. Mrad IB, Mrad MB, Besbes B, Zairi I, Kahla NB, Kamoun S, et al. Heart rate variability as an indicator of autonomic nervous system disturbance in Behcet's Disease. Int J Gen Med. 2021 Aug 27;14:4877-86. doi: 10.2147/IJGM.S326549. PMID: 34475779; PMCID: PMC8407672.
16. Sirichand S, Killu AM, Padmanabhan D, Hodge DO, Chamberlain AM, Brady PA, et al. Incidence of idiopathic ventricular arrhythmias: a population-based study. Circ Arrhythmia Electrophysiol. 2017 Feb;10(2):e004662. doi: 10.1161/CIRCEP.116.004662. PMID: 28183845; PMCID: PMC5319731.
17. Liman NG, Raharjo SB, Timan IS, Suyatna FD, Harris S, Prihartono J, et al. Differential profiles of cortisol, components of autonomic nervous system, and self-rated health in premature ventricular contraction: an observational study of three circadian types. Chronobiol Med. 2023;5(3):117-26. doi: 10.33069/cim.2023.0017.
18. Chen HY. Circadian patterns of heart rate turbulence, heart rate variability and their relationship. Cardiol Res. 2011 Jun;2(3):112-8. doi: 10.4021/cr41w. PMID: 28352377; PMCID: PMC5358314.
19. Kim SH, Lim KR, Seo JH, Ryu DR, Lee BK, Cho BR, et al. Higher heart rate variability as a predictor of atrial fibrillation in patients with hypertension. Sci Rep. 2022 Mar 8;12(1):3702. doi: 10.1038/s41598-022-07783-3. PMID: 35260686; PMCID: PMC8904557.
20. Esler M, Lambert G, Esler D, Sari CI, Guo L, Jennings G. Evaluation of elevated heart rate as a sympathetic nervous system biomarker in essential hypertension. J Hypertens. 2020 Aug;38(8):1488-95. doi: 10.1097/HJH.0000000000002407. PMID: 32195820.
21. Seravalle G, Facchetti R, Cappellini C, Annaloro A, Gelfi E, Grassi G. Elevated heart rate as sympathetic biomarker in human obesity. Nutr Metab Cardiovasc Dis. 2022 Oct;32(10):2367-74. doi: 10.1016/j.numecd.2022.07.011. PMID: 35970685.
22. Salavatian S, Yamaguchi N, Hoang J, Lin N, Patel S, Ardell JL, et al. Premature ventricular contractions activate vagal afferents and alter autonomic tone: implications for premature ventricular contraction-induced cardiomyopathy. Am J Physiol Heart Circ Physiol. 2019 Sep 1;317(3):H607-H616. doi: 10.1152/ajpheart.00286.2019. PMID: 31322427; PMCID: PMC6766725.
23. Mahmood A, Ahmed K, Zhang Y. β-adrenergic receptor desensitization/down-regulation in heart failure: a friend or foe? Front Cardiovasc Med. 2022 Jul 1;9:925692. doi: 10.3389/fcvm.2022.925692. PMID: 35845057; PMCID: PMC9283919.
24. Singh N, Moneghetti KJ, Christle JW, Hadley D, Plews D, Froelicher V. Heart rate variability: an old metric with new meaning in the era of using mhealth technologies for health and exercise training guidance. part one: physiology and methods. Arrhythm Electrophysiol Rev. 2018 Dec;7(4):247-55. doi: 10.15420/aer.2018.30.2. PMID: 30588312; PMCID: PMC6304793.