The Prognostic Significance of Frequency and Morphology of Premature Ventricular Complexes during Ambulatory Holter Monitoring

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Background: Multiform premature ventricular complexes (PVCs) are associated with an adverse prognosis in patients with structural heart disease. Very frequent PVCs are associated with ventricular dysfunction. Our hypothesis is that multiform PVCs confer an adverse prognosis in the general population.

Methods: We performed a retrospective cohort study of patients ≥ 18 years old referred to our institution for 24-hour ambulatory Holter monitoring between July 1, 2008 and December 31, 2009. Holters without PVCs or with more frequent ectopy (couplets, triplets, or nonsustained ventricular tachycardia) were excluded. Clinical and adverse event (AE) data ("major adverse cardiovascular event" or new/worsening heart failure) were gathered from chart review. Data was analyzed by PVC frequency (rare, occasional, or frequent) and pattern (uniform or multiform).

Results: A total of 222 patients (43% male, mean age: 55 ± 16 years) were evaluated (median follow-up 2.3 years [IQR: 2.0–2.6]). Median frequency was 2 PVCs per hour (IQR: 1–13). Multiform PVCs were noted in 48%. Patients with multiform PVCs were older, and had a higher prevalence of comorbidities. Thirty-nine AE were noted. Patients with an AE were younger, had a higher prevalence of HTN, diabetes, CAD, CHF, and previous MI. The multiform group had a higher incidence of AE (28%) compared to the uniform group (8%) ($P < 0.001$). Increasing PVC frequency was associated with a higher incidence of AE (8% vs 24% vs 35%, respectively). In Cox regression analyses, the multiform pattern but not frequency predicted AE.

Conclusions: Multiform PVCs were associated with a 4-fold increase in AE in patients referred for ambulatory Holter monitoring.

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Asymptomatic premature ventricular complexes (PVCs) represent a common arrhythmia observed in patients with or without structural heart disease.^{1–4} Increased PVC frequency has been associated with traditional cardiovascular disease risk factors (hypertension, dyslipidemia, and diabetes), and overt coronary artery disease. PVCs have also been observed in patients with left ventricle (LV) dilatation, LV systolic dysfunction,

congestive heart failure (CHF), and are associated with increased mortality.^{3,5–16} Recent studies have concentrated on the prognostic significance of PVC frequency rather than the prognosis associated with a specific PVC morphology. The prognostic value of PVC pattern (uniform vs multiform) has not been extensively investigated. Continuous ambulatory electrocardiogram (ECG) monitoring (Holter) has become widely available in current practice and

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provides valuable data on underlying subclinical rhythm disorders. The aim of this study is to evaluate the prognostic significance of both PVC frequency and morphology revealed on continuous ambulatory ECG monitoring. The hypothesis is that the multiform pattern rather than frequency is the significant prognosticator of adverse event in patients referred for outpatient 24-hour ambulatory Holter monitoring

METHODS

Study Population

This retrospective cohort consisted of patients 18 years of age or older referred for outpatient 24-hour ambulatory ECG monitoring at a large urban tertiary care center institution in New York City. Patients underwent ambulatory recording between July 1, 2008 and December 31, 2009. Patients were referred for Holter monitoring for indications including: palpitations, syncope, and lightheadedness (near-syncope). Complete demographic and clinical variables, as well as outcomes, were gathered from a review of the subjects' outpatient chart. Data was reviewed from time of recording to up to 3.3 years of follow-up. Additional inpatient records were reviewed in the event of hospitalization during the follow-up period.

Technical Details

Holter recording was performed for 24 hours using a 3-channel Philips DigiTrak Plus Holter Monitor Recorder® (Philips Medical Systems, Eindhoven, The Netherlands). Premature ventricular contractions were analyzed and then categorized by frequency and pattern using the built-in Zymed algorithm v2.9.^{17,18} All recordings were analyzed by the electrocardiographic center principal investigator who performed careful manual over-reading to eliminate artifacts and to correct the automated identification of PVCs and their classification by morphology. Follow-up was via outpatient visits at normally scheduled intervals. Emergency department visits or inpatient hospitalizations were also reviewed. Patients were observed up to 3.3 years with a median observation time of 2.3 years. None of the patients had a myocardial injury or infarct within the 6 months preceding their inclusion in the study.

Inclusion/Exclusion Criteria

All adult patients who experienced at least one PVC during the 24-hour monitoring period were included. Patients who were less than 18 years of age, did not complete a full 24-hour monitoring period, or had ventricular couplets, triplets, or non-sustained ventricular tachycardia were excluded. The development of atrial arrhythmias such as atrial fibrillation was not an exclusionary criterion.

Definitions

Patients were divided into two groups based on pattern: uniform or multiform. Patients with PVCs of a single morphology (uniform) comprised the first group, while the second group included patients with PVCs of at least two morphologies (multiform). PVC frequency was categorized as rare, occasional and frequent: A frequency of <5 PVCs/hour was termed "rare," 5–10 PVCs/hour was deemed "occasional," and >10 PVCs/hour was considered "frequent."

The primary endpoint was the occurrence of a clinically adverse outcome, defined as a major adverse cardiovascular event (MACE) or CHF. MACE included the occurrence of acute coronary syndrome, stroke, or all-cause mortality. Acute coronary syndrome was defined as anginal symptoms (chest discomfort, dyspnea) with or without significant ST-T changes on ECG and/or positive biomarkers. CHF was defined as clinically apparent (CHF; systolic or diastolic etiology).

Ethics

The study was approved by the Beth Israel Medical Center (New York, NY, USA) Institutional Review Board. The requirement for obtaining an informed consent was waived.

Data Compilation

Data was collected by review of an internal electronic database of outpatient visits. Paper charts were also reviewed as needed for supplemental data. Inpatient data was obtained by direct chart review. Holter reports were reviewed electronically from the LifeWatch Connect Website. For patients with missing or incomplete data, charts from the referring physician's office were obtained. Patients with missing or incomplete data by the end of the review process were excluded from the study.

Table 1. Study Population Characteristics

Characteristics	Overall (n = 222)	Uniform (n = 116)	Multiform (n = 106)	P	Rare (n = 132)	Occasional (n = 25)	Frequent (n = 65)	P
Follow-up (year)	2.29 (1.97–2.60)	2.32 (2.08–2.88)	2.21 (1.39–2.58)	0.009	2.32 (2.05–2.61)	2.36 (1.84–2.89)	2.10 (0.78–2.52)	0.007
Age (year)	55 ± 16	52 ± 16	58 ± 16	0.003	50 ± 16	66 ± 10	61 ± 14	<0.001
Male	96 (43%)	48 (41%)	48 (45%)	0.558	60 (45%)	11 (44%)	25 (38%)	0.646
Frequency (PVC/hour)	2 (1–13)	1 (1–4)	7 (1–17)	<0.001	1 (1–1)	7 (5–9)	33 (15–153)	<0.001
Avg HR (bpm)	76 ± 12	77 ± 12	75 ± 11	0.206	77 ± 12	74 ± 10	76 ± 12	0.458
Min HR (bpm)	50 ± 10	50 ± 11	49 ± 9	0.349	49 ± 9	50 ± 8	50 ± 12	0.578
Max HR (bpm)	130 ± 22	133 ± 24	127 ± 20	0.053	134 ± 23	125 ± 17	123 ± 21	0.001
HR Variability (millisecond)	135 ± 52	132 ± 54	138 ± 49	0.368	138 ± 54	130 ± 33	131 ± 53	0.537
CAD	35 (16%)	12 (10%)	23 (22%)	0.020	9 (7%)	8 (32%)	18 (28%)	<0.001
HTN	109 (49%)	50 (43%)	59 (56%)	0.062	50 (38%)	20 (80%)	39 (60%)	<0.001
DM	38 (17%)	19 (16%)	19 (18%)	0.760	16 (12%)	5 (20%)	17 (26%)	0.045
DL	73 (33%)	36 (31%)	37 (35%)	0.540	32 (24%)	9 (36%)	32 (49%)	0.002
DHF	22 (10%)	8 (7%)	14 (13%)	0.116	10 (8%)	3 (12%)	9 (14%)	0.358
SHF	15 (7%)	4 (4%)	11 (10%)	0.040	3 (2%)	2 (8%)	10 (15%)	0.003
MI	11 (5%)	2 (2%)	9 (8%)	0.028	2 (2%)	3 (12%)	6 (9%)	0.008
Smoking	31 (14%)	15 (13%)	16 (15%)	0.642	14 (11%)	3 (12%)	14 (22%)	0.110
Alcohol	41 (18%)	19 (16%)	22 (21%)	0.401	22 (17%)	3 (12%)	16 (25%)	0.271
FHx	53 (24%)	23 (20%)	30 (28%)	0.139	30 (23%)	2 (8%)	21 (32%)	0.047
Aspirin	86 (39%)	41 (35%)	45 (42%)	0.278	39 (30%)	16 (64%)	31 (48%)	0.001
Clopidogrel	12 (5%)	2 (2%)	10 (9%)	0.011	2 (2%)	3 (12%)	7 (11%)	0.008
Statin	82 (37%)	37 (32%)	45 (42%)	0.104	36 (27%)	13 (52%)	33 (51%)	0.002
Beta blocker	66 (30%)	25 (22%)	41 (39%)	0.005	29 (22%)	10 (40%)	27 (42%)	0.009
ACEI/ARB	77 (35%)	34 (29%)	43 (41%)	0.078	31 (23%)	17 (68%)	29 (45%)	<0.001
CCB	44 (20%)	17 (15%)	27 (25%)	0.044	21 (16%)	9 (36%)	14 (22%)	0.064
Adverse event	39 (18%)	9 (8%)	30 (28%)	<0.001	10 (8%)	6 (24%)	23 (35%)	<0.001

Continuous variables are reported as mean ± standard deviation if normally distributed, median (range) if not. Categorical variables are reported as frequency (percentage). Avg HR = average heart rate; Min HR = minimal heart rate; Max HR = maximal heart rate; HR Variability = heart rate variability; CAD = coronary artery disease; HTN = hypertension; DM = diabetes mellitus; DL = dyslipidemia; DHF = diastolic heart failure; SHF = systolic heart failure; MI = previous myocardial infarction; FHx = family history of coronary artery disease; CCB = calcium channel blocker; ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. P < 0.05 are in boldface.

Statistical Analysis

Data were analyzed using Stata version 11.2 (StataCorp, College Station, TX). Categorical data were analyzed using chi-square or Fisher's exact tests. Continuous variables whose distribution followed normality assumptions were analyzed using the Student's *t*-test and Analysis of Variance. Variables whose distribution did not approximate normality were analyzed using the nonparametric Wilcoxon rank-sum and Kruskal-Wallis tests. Kaplan-Meier survival curves were used to analyze survival data (time to adverse event). The log-rank test was used to compare survival curves. A Cox proportional hazards model was used to determine multivariate predictors of time to adverse event. The full model included all the variables that were assessed in the univariate and bivariate analyses and then proceeded through

a backward elimination process to provide the parsimonious model. Note that P < 0.05 were considered statistically significant.

RESULTS

Of the 419 patients who were referred for Holter monitoring 244 met the inclusion criteria. Of these 244 subjects, 22 had missing or incomplete data and were excluded from the final analysis. A total of 5,328 hours of ambulatory ECG monitoring were recorded. The median follow-up time was 2.3 years (IQR: 2.0–2.6). Ninety-five percent (n = 212) of the patients were referred for a chief complaint of palpitations. The patients' baseline characteristics are listed in Table 1. Forty-three percent (n = 96) of the subjects were males. The median frequency of PVCs was 2/hour (IQR: 1–13). The multiform

Table 2. Patients Characteristics across Outcome

Characteristics	Adverse Outcome n = 39	No Adverse Outcome n = 183	P
Follow-up (year)	0.62 (0.35–1.23)	2.38 (2.13–2.89)	<0.001
Age (year)	66 ± 11	52 ± 16	<0.001
Male	21 (54%)	75 (41%)	0.141
Frequency (PVC/hour)	14 (4-93)	1 (1-9)	<0.001
Avg HR (bpm)	77 ± 13	76 ± 11	0.624
Min HR (bpm)	54 ± 12	49 ± 9	0.007
Max HR (bpm)	121 ± 24	132 ± 22	0.004
HR Variability (millisecond)	121 ± 48	138 ± 52	0.053
CAD	16 (41%)	19 (10%)	<0.001
HTN	31 (79%)	78 (43%)	<0.001
DM	16 (41%)	22 (12%)	<0.001
DL	17 (44%)	56 (31%)	0.117
DHF	11 (28%)	11 (6%)	<0.001
SHF	10 (26%)	5 (3%)	<0.001
MI	5 (13%)	6 (3%)	0.027
Smoking	7 (18%)	24 (13%)	0.429
Alcohol	7 (18%)	34 (19%)	0.927
FHx	9 (23%)	44 (24%)	0.898
Aspirin	22 (56%)	64 (35%)	0.013
Clopidogrel	6 (15%)	6 (3%)	0.008
Statin	26 (67%)	56 (31%)	<0.001
Beta-blocker	23 (59%)	43 (24%)	<0.001
ACEI/ARB	25 (64%)	52 (28%)	<0.001
CCB	12 (31%)	32 (17%)	0.059

Continuous variables are reported as mean ± standard deviation if normally distributed, median (range) if not. Categorical variables are reported as frequency (percentage). Avg HR = Average heart rate; Min HR = minimal heart rate; Max HR = maximal heart rate; HR Variability = heart rate variability; CAD = coronary artery disease; HTN = hypertension; DM = diabetes mellitus; DL = dyslipidemia; DHF = diastolic heart failure; SHF = systolic heart failure; MI = previous myocardial infarction; FHx = family history of coronary artery disease; CCB = calcium channel blocker; ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. P < 0.05 are in boldface.

group represented 48% (n = 106) of the overall population. Five percent (n = 11) of the patients had prior myocardial infarction (MI). During this period, 39 adverse events (15 MACE, 24 new or worsening heart failure) were recorded. No deaths or strokes were noted. Subjects' characteristics by outcome are listed in Table 2.

On average, patients with multiform PVCs were older, had a higher prevalence of traditional cardiovascular risk associated comorbidities and were more likely to be taking cardiovascular medication than those in the uniform group (Table 1). Patients in the multiform group also had a higher

Table 3. Outcome across Pattern and Frequency

	Adverse Outcome n = 39	No Adverse Outcome n = 183	P
Uniform (n = 116)	9 (8%)	107 (92%)	<0.001
Multiform (n = 106)	30 (28%)	76 (72%)	
Rare (n = 132)	10 (8%)	122 (92%)	<0.001
Occasional (n = 25)	6 (24%)	19 (76%)	
Frequent (n = 65)	23 (35%)	42 (65%)	

P < 0.05 are in boldface.

occurrence of adverse events (28% vs 8%, P < 0.001; Table 3). Their 3-year event rate was also greater (29.1% vs 7.5%; P < 0.001; Fig. 1). In patients without previous MI those with multiform PVCs fared worse (27% vs 7%; P < 0.001). In a multivariable Cox regression analysis multiform PVCs were found to be a statistically significant and a clinically meaningful predictor of adverse outcome independently of other covariates, along with age, history of diabetes mellitus, and heart failure (systolic and diastolic; Table 4). The results were similar after adjusting for coronary artery disease and prior MI (HR = 3.05 [1.39–6.70; P = 0.005]).

Across frequency groups, an increasing trend in the occurrence of adverse events was observed with the rare group having the lowest occurrence (8%) followed by the occasional (24%) and frequent ones (35%) (P < 0.001; Table 3). The 3-year event rate was also related to frequency (8.1% vs 24.0% and 35.4%, respectively; P < 0.001; Fig. 1). When accounting for morphology this trend was not observed among patients in the uniform group (P = 0.131) but remained valid among patients with multiform PVCs (P = 0.002). A significant association was noted between multiform morphology and higher frequencies of PVCs (18% occasional and 41% frequent vs 5% and 19%, respectively in the uniform group; P < 0.001). In a multivariable Cox regression analysis frequency was not found to be a statistically significant predictor of adverse event whether examined as rare, occasional and frequent or dichotomized at the 5 or at the 10 PVCs/hour cutoff.

DISCUSSION

This study demonstrated that patients with multiform PVCs were at a 4-fold increased risk for

Figure 1. Time to adverse event by frequency (top) and pattern (bottom).

adverse outcomes over 3 years in comparison to those with uniform PVCs regardless of frequency. Also noted was a trend for patients with occasional or frequent PVCs towards increased risk for adverse outcomes in comparison with those with only rare PVCs. In subgroup analyses, this trend was only preserved in the multiform group. The increased risk remained significant after correction for conventional risk factors including indicators of structural heart disease such as history of heart

failure and previous infarct. Multiform PVCs were likely the major determinant of adverse events, the impact of frequency being dependent on the presence of multiple PVC morphologies. Noticeably a majority of subjects who developed adverse events (59%) were on beta-blocker therapy and yet had a higher minimal heart rate compared to the event-free group. This raises the question of the optimality of treatment in these pharmacologically treated patients.

Table 4. Cox Proportional Hazards Analysis

Model	Hazard Ratio (95% CI)	P
Multiform	3.18 (1.46–6.96)	0.004
Age	1.03 (1.00–1.06)	0.032
DM	3.84 (1.95–7.58)	<0.001
DHF	4.05 (1.85–8.89)	<0.001
SHF	8.00 (3.61–17.74)	<0.001

*DM = diabetes mellitus; DHF = diastolic heart failure; SHF = systolic heart failure.

The prognostic significance of multifocal PVCs in an ambulatory setting remains unclear. Lown and Wolf¹⁹ previously discussed multiform PVCs in their study. In their grading, they mentioned multiform PVCs without clearly defining multiformity, and in their results placed them in the same group as occasional isolated PVCs (<10/hour) and frequent ones (>10/hour) reporting one composite end result for this grouping versus couplets and ventricular tachycardia. Maggioni et al.²⁰ in the GISSI-2 study discussed the negative prognosis associated with complex ventricular arrhythmias, but their definition of complexity included a frequency of >10 PVC/hour, couplets, or nonsustained ventricular tachycardia. In addition, the subjects in both aforementioned studies were in the acute post-MI period. The study by Gallagher et al.²¹ on 2332 unselected patients undergoing outpatient Holter monitoring found that the number of PVC morphologies predicted all-cause mortality.

Using the new algorithms of Holter monitors previously discussed, we were able to differentiate the morphology of ventricular activity. This provided a better outlook on multiformity and consequently on its prognostic significance. To date, most large studies of ventricular arrhythmias in healthy subjects were based on short-term ECG monitoring of 1 hour or less^{6,8} and have studied the significance of PVCs at certain predefined frequencies, usually in association with other complex arrhythmias in composite groups.^{6,8,22–24} Massing et al.¹⁵ in their study of the ARIC patient population reported that those with PVCs had increased risk for outcomes (coronary heart disease [CHD] events, fatal CHD, all cause death) compared to those without. That study was based on supine 12-lead ECG at rest and a 2-minute 3-lead rhythm strip and did not address the frequency of PVCs, but rather the mere presence of PVCs during the recording period. Sajadieh et al.¹⁶ used 48-hour ECG monitoring to assess for the impact of the

frequency of PVCs. They found that the detection of a single PVC on resting ECG was associated with a 70% risk for frequent (30 or more per hour) PVCs, ventricular couplets, and runs of four or more PVCs (NSVT). They also reported that middle-aged and elderly subjects with no apparent cardiac disease and increased ventricular ectopic activity of 30 or more PVCs per hour are at a greater than 2.5-fold increased risk for death or acute MI (AMI) over 5 years compared to patients with less than 30 PVCs/hour.

The results of the current study pertaining to frequency agree with those of the Framingham study,⁸ the Multiple Risk Factor Intervention Trial (MRFIT) study,⁶ the Swedish study of men born in 1914,²⁴ and the Copenhagen Holter study¹⁶ concerning increasing risk associated with frequent PVCs, with some exceptions. In all previous studies, frequent PVCs were defined as <30/hour, >30/hour, or >60/hour. This is in line with the model suggested by Lown and Wolf¹⁹ in 1971 for the gradation of PVC frequency, mostly based on empirical experience with patients with AMIs. Our study found a sizable increase in risk at a much lower threshold (5 PVCs/hour). The reason for this wide difference in frequency is not clear. Our data disagrees with previous studies of more elderly populations often in smaller sized cohorts,²³ which did not show an unfavorable prognosis with frequent PVCs, except for when patients also had increased cardiovascular risks.

Exact mechanisms linking PVCs to adverse outcomes remain unclear. Moulton et al.²⁵ using 12-lead ECGs documented a correlation between PVC morphology and structural cardiac disease. One reason for these associations may be that increased complexity of ectopic ventricular activity may be related to subclinical organic heart disease causing heterogeneity in myocardial excitability and refractoriness. Another possible mechanism may be a primary undiagnosed electrophysiological condition or abnormality that predisposes to malignant arrhythmias. This proposed mechanism suggests that the ectopic impulse has a tortuous pathway predisposing the signal to reentry and self-sustaining activity. Multiformity seems to be a harbinger of cardiac damage, implying impaired myocardial functionality to a higher degree than an increased frequency of ventricular ectopic activity. There is little evidence that control of traditional risk factors decreases the prevalence of PVCs or the adverse events associated with them. PVC

suppression with pharmacologic agents, especially prophylactically post-MI, has been previously shown to be harmful.²⁶⁻²⁸ Radiofrequency catheter ablation (RFA) was shown to be beneficial only in patients with dilated cardiomyopathy or with right ventricular outflow tract PVCs.^{11,12} Unfortunately multiform PVCs are unlikely to be responsive to RFA because of the likely plurality of foci. Therefore the most useful suppressive option would probably be pharmacologic in nature. In light of these findings studies are indicated to explore the efficacy and side effects of pharmacologic and ablative therapies on the outcomes of patients with multiform PVCs.

The findings of this study have to be taken within the context of its limitations. Retrospective studies inherently entail a selection bias as our patient population consisted of individuals seen regularly for standard of care reasons or hospitalizations but not specifically for the study purposes, as would have been the case when this was a prospective investigation. Reviewing all consecutive patients who underwent Holter monitoring introduced the possibility of a confounding bias especially in view of the likely heterogeneity of the study population, the common denominator being referral for outpatient Holter monitoring. Attempts to reduce the impact of these elements were made through various statistical analyses, including the multivariable Cox model. This study excluded subjects with ventricular couplets, triplets, or nonsustained ventricular tachycardia despite the prognostic importance of these arrhythmias. This was consistent with our aim, that is, studying the independent impact of the frequency and morphology of PVCs. The result of this exclusion is likely a bias towards the null, so if anything it decreased our effect size but the results were still statistically significant. The sample size was relatively small and the duration of observation was only around 3 years but the statistical power of the study was adequate.

Overall, this study found that in patients referred for ambulatory Holter monitoring those with multiform ventricular ectopy were at a higher risk of having adverse outcomes than subjects with uniform activity. Increased frequency was also a contributing factor, but not statistically significant in the final analysis. While we advocate for a larger prospective study with a longer duration of observation to reinforce our findings, we believe that patients with multiform PVCs should warrant

a heightened clinical awareness with regard to their cardiovascular risk assessment, especially if their PVCs are frequent. As there are no studies that have assessed the risk/benefit ratio of suppression therapy in this specific group, we recommend a more aggressive management of their cardiovascular risk factors until further input is available.

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