Prognostic Significance of PVCs and Resting Heart Rate

Gregory Engel, M.D.,* Shaun Cho, M.D.,† Afshin Ghayoumi, M.D.,‡
Takuya Yamazaki, M.D.,§ Sung Chun, M.D.,§ William F. Fearon, M.D.,*
Victor F. Froelicher, M.D.§

From the Division of Cardiovascular Medicine, Stanford University Medical Center, Stanford, CA; † John Muir Medical Center, Walnut Creek, CA; ‡Mercy Medical Center/UC Davis, Merced, CA; § The Veterans Affairs Palo Alto Health Care System, Palo Alto, CA

Background: We sought to evaluate the prognostic significance of premature ventricular contractions (PVCs) on a routine electrocardiogram (ECG) and to evaluate the relationship between heart rate and PVCs.

Methods: Computerized 12-lead ECGs of 45,402 veterans were analyzed. Vital status was available through the California Health Department Service.

Results: There were 1731 patients with PVCs (3.8%). Compared to patients without PVCs, those with PVCs had significantly higher all-cause (39% vs 22%, P < 0.001) and cardiovascular mortality (20% vs 8%, P < 0.001). PVCs remain a significant predictor even after adjustment for age and other ECG abnormalities. The presence of multiple PVCs or complex morphologies did not add significant additional prognostic information. Those patients with PVCs had a significantly higher heart rate than those without PVCs (mean ± SD: 78.6 ± 15 vs 73.5 ± 16 bpm, P < 0.001). When patients were divided into groups by heart rate (<60, 60–79, 80–99 and >100 bpm) and by the presence or absence of PVCs, mortality increased progressively with heart rate and doubled with the presence of PVCs. Using regression analysis, heart rate was demonstrated to be an independent and significant predictor of PVCs.

Conclusions: PVCs on a resting ECG are a significant and independent predictor of all-cause and cardiovascular mortality. Increased heart rate predicts mortality in patients with and without PVCs and the combination dramatically increases mortality. These findings together with the demonstrated independent association of heart rate with PVCs suggest that a hyperadrenergic state is present in patients with PVCs and that it likely contributes to their adverse prognosis.

A.N.E. 2007;12(2):121–129

premature ventricular contractions; heart rate; electrocardiogram

Premature ventricular contractions (PVCs) are common electrocardiographic findings in patients with and without structural heart disease. Prior evidence suggests that the presence of PVCs has prognostic value but it is unclear what underlying process they represent. A surprising observation in some studies has been an apparent association between higher mean resting heart rates and the presence of PVCs. Activation of the sympathetic nervous system is an important factor in the genesis of ventricular arrhythmias.[1,2] Enhanced automaticity, triggered activity, and reentry are all mechanisms generating rhythm abnormalities; all three mechanisms are markedly potentiated by the action of catecholamines. We sought to make use of our large database of electrocardiogram (ECG) data to confirm the prognostic significance of PVCs and analyze the interaction between heart rate and PVCs. We hypothesized that both elevated heart rate and the presence of PVCs are markers of sympathetic nervous system (SNS) activity and would, therefore, be correlated with each other and predictive of mortality. This would support the other lines of evidence suggesting that the sympathetic nervous system is active in the genesis of PVCs.

METHODS

Study Population

All initial ECGs of consecutive veterans (outpatient and inpatient) who obtained ECGs for any reason at the Palo Alto VA Medical Center from April 1987 until December 1999 were considered in the study. From these 46,959 ECGs, those with atrial fibrillation and paced rhythms were excluded, leaving 45,402 for analysis.

Electrocardiography

Computerized 12-lead resting 10-second ECG recordings were digitally recorded on the Marquette MAC system. Only the initial ECG was considered for patients with multiple ECGs in the database. Most of the ECG analysis was performed using the GE/Marquette ECG analysis program (www.gemedicalsystems.com). PVCs were defined as at least one QRS complex that was premature, ectopic shaped and had a QRS duration of greater than 120 ms. All ECGs classified as having PVCs were manually over-read by two cardiologists. Of the ECGs originally classified as having PVCs present, 14% were found to be misclassified as having PVCs when none were present. The most common reason for these errors was misclassification of artifact or of aberrantly conducted supraventricular beats. All the misclassified patients were reclassified into the "PVC absent" group, leaving 1731 patients for analysis in the "PVC present" group.

The "PVC present" ECGs were then reviewed to categorize the patterns and morphologic characteristics of confirmed PVCs. These characteristics included presence of multiple PVCs on a single 10-sec ECG, presence of couplets or salvos (≥3 consecutive PVCs), presence of bigeminal or trigeminal rhythm, and presence of multiform PVC morphologies. For the purposes of this study, complex PVCs were defined as repetitive PVCs (≥2 consecutive) and multiform morphologies. Non-sustained ventricular tachycardia was rarely documented on these short recordings and the few short runs of 3 or more consecutive beats were not analyzed separately.

Heart rate was determined by the program by counting all QRS complex templates in 10 seconds and multiplying by six. When PVCs were present, the R-R interval between the normal, dominant sinus QRS complexes (NN) was manually measured except when the pattern of PVCs made it impossible (i.e., bigeminy). This NN interval was used to calculate the intrinsic sinus rate.

An "abnormal" ECG was defined as the presence of one or more of the following: pathologic Q waves, left or right bundle branch block, intraventricular conduction delay, Wolff–Parkinson–White syndrome, right or left ventricular hypertrophy (Romhilt–Estes), left atrial enlargement, or abnormal ST segments. All remaining ECGs were classified as "normal."

Follow-UP

The Social Security Death Index and California Health Department Service were used to ascertain vital status as of 12/31/00. Cause of death was available from the later and deaths determined by the Social Security Death Index were classified by review of the Veterans' Affairs clinical data base. All-cause death and cardiovascular death were used as endpoints. Mean follow-up was 5.5 years. Data regarding cardiac interventions or events was not available.

Statistical Methods

Number Crunching System Software (Kaysville, UT) was used for all statistical analyses after transferring the data from a Microsoft ACCESS (Redmond, WA, USA) database. Unpaired 2-tailed t tests were used for univariate comparison of variables. Cox proportional hazard analysis was performed to evaluate those with and without PVCs and those with multiple and complex PVCs. Multivariate Cox hazard function analysis was performed to demonstrate if the various PVC characteristics were independently and significantly associated with time until death after considering age and other ECG abnormalities. Analysis was repeated using data from only those patients with normal ECGs. Kaplan–Meier survival analysis was again performed after patients were divided into groups by heart rate (<60, 60–79, 80–99 and >100 bpm) and by the presence or absence of PVCs. Multiple regression analysis was performed with heart rate as the dependent variable and with the following independent variables: age, gender, abnormal/normal ECG classification, in- or outpatient status and PVCs present or not. Logistic regression was performed with PVCs as the dependent variable and with the following independent variables: age, gender,

Table 1. Demographics and ECG Findings in Patients with and without PVCs

Variable	Total N = 45,402	No PVCs N = 43,671	PVCs N = 1,731 (3.8%)	P-Value
Demographics				
Age	56 ± 15	56 ± 15	65 ± 12	<0.001
Males	90.0%	90%	94%	0.01
Height	69 ± 4	69 ± 4	69 ± 4	0.3
Weight	182 ± 40	182 ± 40	184 ± 41	0.1
BMI	27 ± 6	27 ± 6	27 ± 6	0.4
Outpatients	73%	73%	70%	0.004
ECG findings				
Heart rate	73.7 ± 16	73.5 ± 16	78.6 ± 15	<0.001
Q wave	13%	11%	23%	<0.001
LVH	5%	5%	8 %	<0.001
RVH	0.3%	0.3%	0.3%	0.6
RBBB	4%	3%	7%	<0.001
LBBB	1%	1%	3%	<0.001
LAE	4%	3.8%	10.7%	<0.001
Abnormal ECG	24%	23%	43%	<0.001

Age, height (inches), weight (pounds), BMI and heart rate are presented as the mean ± SEM.
BMI = body mass index; ECG = electrocardiogram; LAE = left atrial enlargement; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; PVC = premature ventricular contraction; RBBB = right bundle branch block; RVH = right ventricular hypertrophy

abnormal/normal ECG classification, PVCs present or absent and in- or outpatient status.

RESULTS

After exclusion of patients with atrial fibrillation and paced rhythms, there were 43,671 patients without PVCs and 1731 patients with PVCs (3.8%). Demographic and ECG characteristics of the groups are shown in Table 1. The group with PVCs was older than those without PVCs (mean age ± SD: 65 ± 12 vs 56 ± 15, P < 0.001). As this was a VA study, the patients are 90% male but there was a slightly higher percentage of men among those with PVCs (90% vs 94%, P = 0.01). There were no significant differences between height, weight or BMI. Patients with PVCs had a significantly higher prevalence of Q waves, LVH, LAE, bundle branch blocks and ECGs classified as abnormal. Of the ECG characteristics evaluated, only RVH was similar between the groups.

Those patients with PVCs had a significantly higher heart rate than those without PVCs (mean ± SD: 78.6 ± 15 vs 73.5 ± 16 bpm, P < 0.001). This heart rate difference persisted when patients were subgrouped by gender, race, outpatient versus inpatient status and those with otherwise normal ECGs (i.e., least likely to have structural heart disease). Those patients with PVCs always had a significantly higher mean heart rate. Further analysis of heart rate differences showed that women had a significantly lower mean HR than men (71.1 ± 13.7 vs 74.0 ± 16.2, P < 0.001), outpatients had a lower mean heart rate than inpatients (72.5 ± 15.0 vs 76.9 ± 17.7, P < 0.001), and those with an otherwise normal ECG had a lower heart rate than those with an abnormal ECG (73.2 ± 15.6 vs 75.2 ± 16.8, P < 0.001).

Multiple PVCs (≥2 PVC per ECG) were present in 47% patients with PVCs. Of these 10% were couplets or salvos, 21% had multiform morphologies, and 15% had ventricular bigeminal or trigeminal patterns. The demographics and prevalence of ECG abnormalities for these patients are shown in Table 2. Patients with multiple PVCs were older than those with only single PVCs present on the ECG. Those with complex forms were older than those with noncomplex morphologies. There were no statistically significant differences in the prevalence of Q waves, LVH, right or left bundle branch block between those patients with or without multiple PVCs. Patients with complex PVCs had statistically significantly more Q waves on their ECGs than those without complex PVCs (P = 0.007).

The average annual all-cause mortality in the total population was 3.9% with mortality in those with PVCs (6.7%) significantly higher than for those without PVCs (3.8%) (Table 3). The average annual

Table 2. Demographics and ECG Findings in Patients with Single Versus Multiple and Noncomplex Versus Complex PVCs

Variable	Single PVCs 911 (53%)	Multiple PVCs 815 (47%)	P-Value	Noncomplex PVCs 1527 (88%)	Complex PVCs 199 (12%)	P-Value
Demographics						
Age	65 ± 12	66 ± 11	0.05	65 ± 12	68 ± 10	<0.001
Height	69 ± 3	69 ± 3	0.26	69 ± 3	70 ± 3	0.30
Weight	186 ± 39	186 ± 39	>0.9	186 ± 39	184 ± 37	0.52
BMI	27 ± 6	27 ± 6	0.4	27 ± 6	27 ± 6	0.36
Outpatients	68%	68%	0.89	68%	67%	0.68
ECG findings						
Heart rate	77 ± 16	81 ± 15	<0.001	79 ± 16	84 ± 14	<0.001
Q wave	25%	23%	0.32	23%	31%	0.007
LVH	8 %	9%	0.59	8%	11%	0.18
RVH	0.3%	0.5%	0.60	0.3%	1.5%	0.009
RBBB	7%	7%	0.81	7%	7%	0.85
LBBB	3%	3%	0.77	3%	3%	0.81
LAE	10%	11%	0.81	10.5%	10.6%	>0.9
Abnormal ECG	48%	47%	0.72	47%	54%	0.04

Age, height (inches), weight (pounds), BMI and heart rate are presented as the mean ± SEM.
BMI = body mass index; ECG = electrocardiogram; LAE = left atrial enlargement; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; PVC = premature ventricular contraction; RBBB = right bundle branch block; RVH = right ventricular hypertrophy.

CV mortality in the total population was 1.5% (39% of the deaths) with CV mortality in those with PVCs (3.5%) significantly higher than for those without PVCs (1.4%). Those with complex PVCs had an annual CV mortality rate of 5.1%. The hazard ratios for patients with all types of PVCs were significantly increased when compared to patients having no PVCs on an ECG. The age-adjusted hazard ratios in patients with any PVCs versus those with no PVCs was 1.39 (95% CI 1.29–1.50) for all cause mortality and 1.81 (95% CI 1.62–2.01) for cardiovascular mortality. There was no statistically significant difference in mortality between patients who had multiple (≥2) PVCs per ECG and those with only single PVCs. The age-adjusted hazard ratio for complex PVCs (vs no PVCs) for all-cause and cardiovascular mortality in all patients was 1.6 (95% CI 1.3–

1.9) and 2.1 (95% CI 1.6–2.8), respectively. Patients with complex PVCs appeared to have increased all-cause and CV mortality as compared to those with non-complex PVCs but the difference in survival did not achieve statistical significance. Similar findings resulted when the analysis was limited to patients with normal resting ECGs. After considering age, BMI, and ECG findings in a Cox hazard model, the presence of any resting PVCs were found to be independent predictors of mortality with a hazard ratio of 2.0 (95% CI 1.1–2.8)

When patients were divided into groups by heart rate (<60, 60–79, 80–99 and >100 bpm) and by the presence or absence of PVCs, mortality increased progressively with heart rate and doubled with the presence of PVCs (Table 4, Fig. 1). Cardiovascular mortality ranged from a low of 6.3% in those

Table 3. Mortality in Patients with and Without PVCs

	Total N = 45,402	No PVCs N = 43,671	PVCs N = 1,731 (3.8%)	P-Value
All-cause mortality	23%	22%	39%	<0.001
Annual all-cause mortality	3.9%	3.8%	6.7%	<0.001
CV mortality	8.3%	7.9%	19.6%	<0.001
Annual CV mortality	1.5%	1.4%	3.5%	<0.001

CV = cardiovascular; PVC = premature ventricular contraction.

Table 4. Cardiovascular Mortality by Heart Rate Group

	Heart Rate <60	Heart Rate 60–79	Heart Rate 80–99	Heart Rate >99
		Without PVCs		
No. of patients	8,077	22,090	10,677	2,827
CV mortality (%)	6.3	7.3	9.4	11.3
Annual CV mortality (%)	1.1	1.3	1.7	2.0
		With PVCs		
No. of patients	150	832	596	153
CV mortality (%)	12.0	17.1	23.3	26.1
Annual CV mortality (%)	2.2	3.1	4.2	4.7

CV = cardiovascular; PVC = premature ventricular contraction.

with heart rates less than 60 bpm and no PVCs to a high of 26.1% in those with a heart rate > 100 bpm and PVCs. Within each heart rate group, there was a significant increase in mortality when PVCs were present (P < 0.001). The differences in event free survival between groups is also clearly demonstrated with Kaplan–Meier cumulative survival curve (Fig. 2). The PVC and heart rate stratifications performed similarly when patients were divided into those with normal and abnormal ECGs. Cox regression analysis (controlled for age, gender, outpatient vs inpatient status and normal vs abnormal ECG) demonstrates that PVCs (RR 1.61, 95% CI 1.44–1.80, P < 0.001) and heart rate (RR 1.02 for each 1 bpm increase, 95% CI 1.01–1.02, P < 0.001) are independent predictors of cardiovascular mortality.

Logistic regression controlled for age, gender and normal versus abnormal ECG was performed to confirm that heart rate was a significant and independent predictor of the presence of PVCs (OR 1.40 for each 20 bpm, 95% CI 1.33 to 1.48, P < 0.001).

Although patients with PVCs were older than those without PVCs (univariate analysis above), age alone cannot explain the different heart rates because regression analysis showed that resting heart rate did not change significantly with age (slope of less than 1 bpm per decade). When multiple regression analysis was performed to evaluate predictors of heart rate, age did not demonstrate a statistically significant contribution.
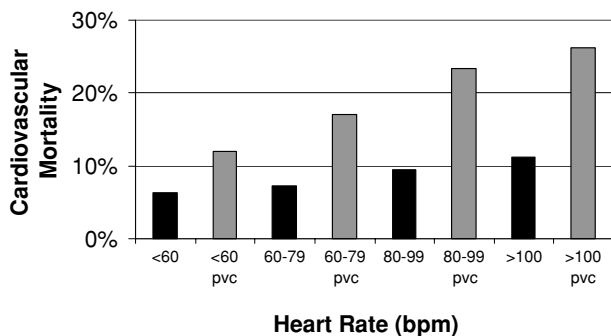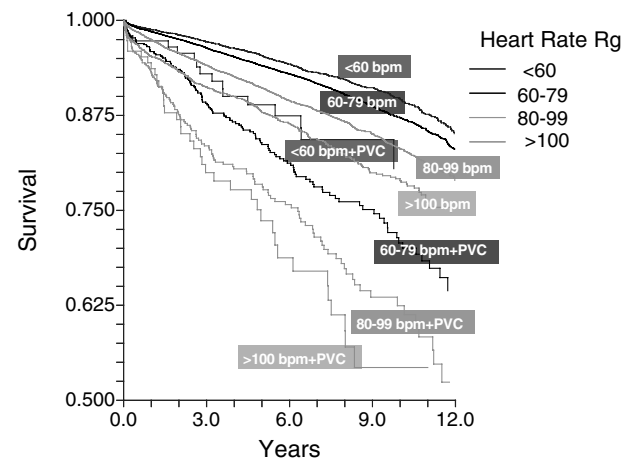

Figure 1. Differences in cardiovascular mortality between patients without PVCs (black) and those with PVCs (gray) are shown. Within each heart rate group, there is a significant increase in mortality when PVCs are present (P < 0.001). Mortality also increases as heart rate increases in both patients with and without PVCs (P < 0.001). PVC = premature ventricular contraction.

Figure 2. Kaplan–Meier cumulative survival curves demonstrate decreasing survival with increasing heart rate among patients without PVCs and more significant declines in survival in those with PVCs. The curves followed a consistent order with increasing mortality with increasing rate and with the matching color coded line with PVCs exhibiting an increased mortality. PVC = premature ventricular contraction.

DISCUSSION

PVCs

The "PVC hypothesis" that PVC suppression would prevent sudden death was popularized by Lown[3] and others in the 1960s and 1970s and was accepted as dogma well into the late 1980s. It was based on seemingly sound logic that that sudden death in myocardial infarction survivors is due to ventricular fibrillation[4,5] and that PVCs precede and therefore identify those patients who are susceptible to these episodes.[3] It was assumed that the suppression of PVCs with antiarrhythmic drugs would be beneficial but the disappointing results of the CAST trials[6,7] negated the causal role theory of PVCs. In fact, the negating of the "PVC hypothesis" by the CAST results is a classic example of why hypothetical mechanisms cannot replace the evidence based approach. Partly due to these results, PVCs are generally ignored on a routine ECG. But, PVCs may still have an important role in risk stratification even if treatment with antiarrhythmic medications is not appropriate.

A higher prevalence of PVCs has been seen in patients with coronary artery disease,[8] hypertension,[9] accompanying ECG abnormalities,[10] and nearly every form of structural heart disease. PVCs also increase with age.[11,12] In the acute phase of myocardial infarction, PVCs are seen in 80–90% of patients and have been related to residual ischemia,[13] degree of coronary narrowing,[14] degree of left ventricular involvement[15,16] and age of infarction.[17]

In patients without established cardiovascular disease, there have been conflicting findings with some authors concluding that PVCs are benign in this population,[18,19] and others reporting increased mortality,[8,20,21] although the methods used to determine true absence of coronary artery disease varied greatly between studies. Our results are consistent with the Framingham Heart Study of 6,033 men and women who underwent one hour ambulatory electrocardiography.[8] After adjusting for age and traditional risk factors for coronary artery disease, there was a significant and independent association between asymptomatic ectopy in men without clinically apparent coronary heart disease and the risk for all-cause mortality (RR 2.3) as well as death from coronary heart disease (RR 2.1). Such an association was not seen in women or in men with known coronary artery disease.

The idea that looking at the frequency and morphology of PVCs might provide additional predictive power has been investigated. Ismaile et al. reported findings from a prospective study of 15,637 apparently healthy white men who underwent screening for the Multiple Risk Factor Intervention Trial (MRFIT).[21] They used 2 minute resting rhythm strips and concluded that the presence of frequent or complex PVCs is associated with a significant and independent risk for sudden cardiac death (RR 4.2; RR 3.0 for the presence of any PVCs). Our study confirms the risk predicted by any PVC but only shows a non-significant trend towards worse outcome with complex or multiple PVCs. This may be because we looked at all-cause and cardiovascular mortality but did not limit our outcome to sudden death.

Heart Rate

Gillman et al. evaluated 4,530 untreated hypertensives using 36-year follow-up data from the Framingham Study.[22] Regression analysis, after adjustment for age and systolic blood pressure, showed that there was a two-fold increase in cardiovascular mortality for each heart rate increment of 40 beats/min. In a French study of 19,386 subjects undergoing routine health examinations, resting tachycardia was demonstrated to be a predictor of noncardiovascular mortality in both genders, and of cardiovascular mortality in men, independent of age and blood pressure.[23] Heart rate on the initial ECG after acute myocardial infarction has also been shown to be an independent predictor of prognosis.[24] Our results add to the evidence that heart rate is an important prognostic variable.

Several large studies confirm our finding of heart rate not being related to age.[25−28] There are conflicting reports in the literature as to the association of gender and heart rate. Some studies suggest that heart rate is higher in women[25,26] while others confirm our finding of heart rate being lower in women.[28]

PVCs and Heart Rate

Few studies have evaluated the relationship of resting PVCs with increased heart rate on an ECG. The Atherosclerosis Risk In Communities (ARIC) study reported the prevalence of PVCs in 15,792 individuals aged 45–65 years on a longer than normal ECG recording of 2 minutes.[28] PVCs were present in 6% of these middle-aged adults and faster sinus rates were directly related to PVC prevalence.

The relationship of PVCs to heart rate has been described in a series of studies using Holter monitoring. The relationship between the frequency of PVCs and underlying heart rate was reported in patients with frequent PVCs; the most frequent relationship was an increase in PVCs with increasing heart rate.[29,30] It has also been shown that there are three reproducible trends characterizing the dynamic behavior of PVCs: a tachycardia-enhanced pattern (28%), a bradycardia-enhanced pattern (24%), and an indifferent pattern in the remainder of patients (48%).[31] Another study suggested that beta-blockers were most effective in reducing PVC frequency in the tachycardia and indifferent groups.[32] Propafenone has also been shown to be most effective in tachycardia-enhanced patients.[33]

Sympathetic Nervous System Activity

Several lines of evidence suggest that activation of the sympathetic nervous system (SNS) plays a primary role in the generation of PVCs, ventricular arrhythmias and sudden cardiac death.[2,34] Circulating catecholamines and increased heart rate are known to interact with all three major mechanisms involved in the generation of arrhythmias: enhanced automaticity, triggered automaticity, and reentry.[35] Substantial experimental data from animal studies shows that activation of the SNS is a strong stimulus for the development of ventricular tachyarrhythmias. It is well established that medications with beta-blocking properties help to decrease the frequency of PVCs[36] and prevent sudden death.[37,38] Decreased sympathetic tone and improvement of cardiac autonomic regulation appear to play a major role in the ability of beta-blockers to reduce PVCs.[39]

Studies of genetic disorders, animal models, and spontaneous human arrhythmias have helped to create a better understanding of this relationship.[1] Infusion of nerve growth factor into animal models, designed to mimic long-term elevations of sympathetic activity and signaling, resulted in apoptosis, hypertrophy, and fibrosis. In human studies, changes in heart rate have been shown to occur prior to the onset of PVCs and ventricular arrhythmias.[31,40−42] The propensity for PVCs and ventricular arrhythmias is highest when there are superimposed effects of short-, intermediate-, and long-term changes. Parasympathetic inhibition of SNS activity may be part of a normal regulatory process

that is lost in patients with severe heart failure and other disorders.

Some investigators have proposed the nerve sprouting hypothesis of ventricular arrhythmia to explain arrhythmic events seen in patients with a history of myocardial infarction.[43] The theory is that myocardial damage results in nerve injury which is followed by sympathetic nerve sprouting and regionally increased sympathetic tone. The increased SNS activity in the local area of remodeled myocardium results in PVCs, ventricular tachycardia/fibrillation and sudden death. Support for this hypothesis was provided by an evaluation of cardiac nerves in explanted native hearts of human transplant recipients.[44] Infusion of nerve growth factor into the left stellate ganglion of dogs was also shown to result in increased development of ventricular arrhythmias.[45] The recurring theme of research in this area is that the response to injury results in heterogeneous sympathetic innervation, which is highly arrhythmogenic.[46]

Study Limitations

The population in our study included a relatively diverse group of all consecutive inpatients and outpatients who had a 12-lead ECG for any reason; the only exclusion criteria were the presence of atrial fibrillation or a paced rhythm. This differs from many previous studies of either more narrowly defined high-risk populations of patients referred to electrophysiologists or more broadly defined low-risk community epidemiological cohorts. These differences may be an advantage as our study is clinically based and includes all patients at our facility referred for an ECG. Baseline clinical data, laboratory studies and diagnostic tests such as echocardiograms or cardiac catheterizations were not available. Information on medications, especially beta-blockers, would have been very useful. The ECGs were obtained over the span of more than a decade during which time there were changes in practice patterns and beta-blocker usage. However, there is no reason to think that beta-blocker usage would be less in those with PVCs (such that this would explain their higher heart rate). We also lack other markers of sympathetic activity to confirm our hypothesis. An important limitation of the study is that PVCs are identified on a single 10 second ECG recording. This "snapshot" might not be expected to provide as much clinically meaningful information as longer term ambulatory ECG monitoring but, the

extremely large number of patients available for analysis allows significant results to be obtained. The 4% prevalence of PVCs found in our study compares favorably with a rate of 2–7% in previous epidemiologic studies including those using 2-min rhythm strips.[10,17,28,47]

Overall, this is a retrospective analysis and, as such, should be considered hypothesis generating rather than conclusive evidence of a cause and effect relationship. The predictive models generated here should be validated using other electrocardiographic databases and in prospective evaluations.

CONCLUSIONS

Our study suggests that the simple 12-lead ECG provides valuable information and can complement more advanced strategies for arrhythmic risk stratification. The presence of any PVC on a single ECG is a powerful predictor of all-cause and cardiovascular mortality. The presence of multiple or complex PVCs was not a significantly better predictor although there was a trend towards worse prognosis in patients with complex forms. These observations are true even in those patients with otherwise normal baseline ECGs. Regression analysis demonstrates that heart rate is a significant and independent predictor of the presence of PVCs. Our findings support the hypothesis that activation of the sympathetic nervous system is an important factor in the genesis of PVCs and ventricular arrhythmias. The presence of elevated heart rate is a significant prognostic factor and the combination of increased heart rate and PVCs dramatically increases mortality.

REFERENCES

1. Anderson KP. Sympathetic nervous system activity and ventricular tachyarrhythmias: Recent advances. Ann Noninvasive Electrocardiol 2003;8:75–89.
2. Podrid PJ, Fuchs T, Candinas R. Role of the sympathetic nervous system in the genesis of ventricular arrhythmia. Circulation 1990;82:I103—I113.
3. Lown B, Wolf M. Approaches to sudden death from coronary heart disease. Circulation 1971;44:130–142.
4. Nikolic G, Bishop RL, Singh JB. Sudden death recorded during Holter monitoring. Circulation 1982;66:218–225.
5. Pratt CM, Francis MJ, Luck JC, et al. Analysis of ambulatory electrocardiograms in 15 patients during spontaneous ventricular fibrillation with special reference to preceding arrhythmic events. J Am Coll Cardiol 1983;2:789–797.
6. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989;321:406–412.
7. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. N Engl J Med 1992;327:227–233.
8. Bikkina M, Larson MG, Levy D. Prognostic implications of asymptomatic ventricular arrhythmias: The Framingham Heart Study. Ann Intern Med 1992;117:990–996.
9. Vogt M, Motz W, Scheler S, et al. Disorders of coronary microcirculation and arrhythmias in systemic arterial hypertension. Am J Cardiol 1990;65:45G–50G.
10. Fisher FD, Tyroler HA. Relationship between ventricular premature contractions on routine electrocardiography and subsequent sudden death from coronary heart disease. Circulation 1973;47:712–719.
11. Fleg JL. Ventricular arrhythmias in the elderly: Prevalence, mechanisms, and therapeutic implications. Geriatrics 1988;43:23–29.
12. Kostis JB, McCrone K, Moreyra AE, et al. The effect of age, blood pressure and gender on the incidence of premature ventricular contractions. Angiology 1982;33:464–473.
13. Mukharji J, Rude RE, Poole WK, et al. Risk factors for sudden death after acute myocardial infarction: Two-year follow-up. Am J Cardiol 1984;54:31–36.
14. Minisi AJ, Mukharji J, Rehr RB, et al. Association between extent of coronary artery disease and ventricular premature beat frequency after myocardial infarction. Am Heart J 1988;115:1198–1201.
15. Bigger JT, Jr, Fleiss JL, Kleiger R, et al. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. Circulation 1984;69:250–258.
16. Tracy CM, Winkler J, Brittain E, et al. Determinants of ventricular arrhythmias in mildly symptomatic patients with coronary artery disease and influence of inducible left ventricular dysfunction on arrhythmia frequency. J Am Coll Cardiol 1987;9:483–488.
17. Kostis JB, Byington R, Friedman LM, et al. Prognostic significance of ventricular ectopic activity in survivors of acute myocardial infarction. J Am Coll Cardiol 1987;10:231–242.
18. Fleg JL, Kennedy HL. Long-term prognostic significance of ambulatory electrocardiographic findings in apparently healthy subjects greater than or equal to 60 years of age. Am J Cardiol 1992;70:748–751.
19. Rodstein M, Wolloch L, Gubner RS. Mortality study of the significance of extrasystoles in an insured population. Circulation 1971;44:617–625.
20. Rabkin SW, Mathewson FA, Tate RB. Relationship of ventricular ectopy in men without apparent heart disease to occurrence of ischemic heart disease and sudden death. Am Heart J 1981;101:135–142.
21. Abdalla IS, Prineas RJ, Neaton JD, et al. Relation between ventricular premature complexes and sudden cardiac death in apparently healthy men. Am J Cardiol 1987;60:1036–1042.
22. Gillman MW, Kannel WB, Belanger A, et al. Influence of heart rate on mortality among persons with hypertension: The Framingham Study. Am Heart J 1993;125:1148–1154.
23. Benetos A, Rudnichi A, Thomas F, et al. Influence of heart rate on mortality in a French population: Role of age, gender, and blood pressure. Hypertension 1999;33:44–52.
24. Hathaway WR, Peterson ED, Wagner GS, et al. Prognostic significance of the initial electrocardiogram in patients with acute myocardial infarction. GUSTO-I Investigators. Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries. JAMA 1998;279:387–391.

25. Gillum RF. The epidemiology of resting heart rate in a national sample of men and women: Associations with hypertension, coronary heart disease, blood pressure, and other cardiovascular risk factors. Am Heart J 1988;116:163–174.

26. Morcet JF, Safar M, Thomas F, et al. Associations between heart rate and other risk factors in a large French population. J Hypertens 1999;17:1671–1676.

27. Spodick DH, Raju P, Bishop RL, et al. Operational definition of normal sinus heart rate. Am J Cardiol 1992;69:1245–1246.

28. Simpson RJ, Jr, Cascio WE, Schreiner PJ, et al. Prevalence of premature ventricular contractions in a population of African American and white men and women: The Atherosclerosis Risk in Communities (ARIC) study. Am Heart J 2002;143:535–540.

29. Acanfora D, De Caprio L, Di Palma A, et al. Relationship between ventricular ectopic beat frequency and heart rate: Study in patients with severe arrhythmias. Am Heart J 1993;125:1022–1029.

30. Winkle RA. The relationship between ventricular ectopic beat frequency and heart rate. Circulation 1982;66:439–446.

31. Pitzalis MV, Mastropasqua F, Massari F, et al. Dependency of premature ventricular contractions on heart rate. Am Heart J 1997;133:153–161.

32. Pitzalis MV, Mastropasqua F, Massari F, et al. Holter-guided identification of premature ventricular contractions susceptible to suppression by beta-blockers. Am Heart J 1996;131:508–515.

33. Saikawa T, Niwa H, Ito M, et al. The effect of propafenone on premature ventricular contractions (PVC): An analysis based on heart rate dependency of PVCs. Jpn Heart J 2001;42:701–711.

34. Grassi G, Seravalle G, Bertinieri G, et al. Behaviour of the adrenergic cardiovascular drive in atrial fibrillation and cardiac arrhythmias. Acta Physiol Scand 2003;177:399–404.

35. Stein KM, Karagounis LA, Markowitz SM, et al. Heart rate changes preceding ventricular ectopy in patients with ventricular tachycardia caused by reentry, triggered activity, and automaticity. Am Heart J 1998;136:425–434.

36. Krittayaphong R, Bhuripanyo K, Punlee K, et al. Effect of atenolol on symptomatic ventricular arrhythmia without structural heart disease: A randomized placebo-controlled study. Am Heart J 2002;144:e10.

37. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. JAMA 1982;247:1707–1714.

38. Pedersen TR. Six-year follow-up of the Norwegian Multicenter Study on Timolol after Acute Myocardial Infarction. N Engl J Med 1985;313:1055–1058.

39. Acanfora D, Pinna GD, Gheorghiade M, et al. Effect of beta-blockade on the premature ventricular beats/heart rate relation and heart rate variability in patients with coronary heart disease and severe ventricular arrhythmias. Am J Ther 2000;7:229–236.

40. Anderson KP, Shusterman V, Aysin B, et al. Distinctive RR dynamics preceding two modes of onset of spontaneous sustained ventricular tachycardia. (ESVEM) Investigators. Electrophysiologic Study Versus Electrocardiographic Monitoring. J Cardiovasc Electrophysiol 1999;10:897–904.

41. Nemec J, Hammill SC, Shen WK. Increase in heart rate precedes episodes of ventricular tachycardia and ventricular fibrillation in patients with implantable cardioverter defibrillators: Analysis of spontaneous ventricular tachycardia database. Pacing Clin Electrophysiol 1999;22:1729–1738.

42. Sapoznikov D, Luria MH, Gotsman MS. Changes in sinus RR interval patterns preceding ventricular ectopic beats: Assessment with rate enhancement and dynamic heart rate trends. Int J Cardiol 1999;69:217–224.

43. Chen PS, Chen LS, Cao JM, et al. Sympathetic nerve sprouting, electrical remodeling and the mechanisms of sudden cardiac death. Cardiovasc Res 2001;50:409–416.

44. Cao JM, Fishbein MC, Han JB, et al. Relationship between regional cardiac hyperinnervation and ventricular arrhythmia. Circulation 2000;101:1960–1969.

45. Cao JM, Chen LS, KenKnight BH, et al. Nerve sprouting and sudden cardiac death. Circ Res 2000;86:816–821.

46. Verrier RL, Antzelevitch C. Autonomic aspects of arrhythmogenesis: The enduring and the new. Curr Opin Cardiol 2004;19:2–11.

47. Crow RS, Prineas RJ, Dias V, et al. Ventricular premature beats in a population sample. Frequency and associations with coronary risk characteristics. Circulation 1975;52:III211—III215.