Premature Ventricular Complexes in the Absence of Identifiable Heart Disease

JOHN B. KOSTIS, M.D., KATHRYN MCCARONE, R.N., A. E. MOREYRA, M.D., S. GOTZOYANNIS, M.D., NORA M. AGILTZ, R.N., N. NATARajan, M.D., AND P. T. Kuo, M.D.

SUMMARY To define the prevalence, frequency and characteristics of premature ventricular complexes (PVCs) in adults free of recognizable heart disease, we performed 24-hour ambulatory electrocardiography on 101 subjects (51 men and 50 women, mean age 48.8 years) in whom physical examination, chest x-ray, ECG, echocardiogram, maximal exercise stress test, right- and left-heart catheterization and coronary arteriography were normal. Thirty-nine subjects had at least 1 PVC/24 hours, but only four had more than 100 PVCs/24 hours and fewer than five had more than five PVCs in any given hour. The probability of having at least 1 PVC/24 hours increased with age (chi square = 11.789, p = 0.019). The number of PVCs/24 hours was also positively associated with age (r = 0.33, p = 0.001). There was no consistent relationship between the presence or number of PVCs/24 hours and sex, blood pressure, weight, height, body mass index, serum potassium or calcium, cholesterol and triglyceride, hemoglobin, the ingestion of coffee, tea or alcohol, and cigarette smoking. Four subjects had multiform PVCs, two of whom had early PVCs.

AMBULATORY ELECTROCARDIOGRAPHY is commonly performed to detect frequent or complex ventricular ectopy, especially in patients with coronary artery disease.1-4 However, scant data are available on the incidence, frequency and characteristics of premature ventricular complexes (PVCs) in normal subjects. Kennedy and associates5-6 described a group of apparently healthy subjects with frequent and complex ventricular irritability selected from a large referral population, including subjects with coronary artery disease and elevated left ventricular end-diastolic pressure. Hinkle and associates found PVCs in a high percentage of middle-aged men.7,8 In these studies, many subjects with frequent PVCs also had clinical evidence of coronary heart disease, hypertension or chronic obstructive lung disease, and frequent PVCs were associated with a fatal event in the next few years.

Raftery and Cashman9 found low frequency of PVCs in 53 ambulatory, apparently normal subjects. Brodsky and co-workers10 found PVCs in 25 of 50 apparently normal male medical students, ages 23-27 years, in whom cardiac disease was excluded by noninvasive testing. Clarke and co-workers11 found significant ventricular arrhythmias, including frequent ventricular ectopic beats, R-on-T phenomenon, multifocal ventricular ectopic beats, bigeminy and ventricular tachycardia in 10 of 86 subjects (12%) who were apparently healthy by history, physical examination, electrocardiography, and biochemical and hematological screening. An exercise stress test or coronary arteriography was not performed to exclude coronary artery disease. In a similar study, Glasser and associates12 found PVCs in seven of 13 apparently healthy subjects, ages 62-84 years. Gilson13 found infrequent ventricular ectopic beats in his early studies of apparently normal males.

Because undetected coronary artery disease is prevalent in middle age, and because coronary arteriography was not performed in these studies of apparently normal subjects, coronary atherosclerosis cannot be excluded as a cause of the observed arrhythmias, and these studies cannot be used to define the normal. Using ambulatory monitoring for 10 waking hours, DeMaria and associates14 found PVCs in 10 of 40 subjects with normal cardiac catheterization that were used as the control group in a study of mitral valve prolapse. Details of this group were not reported. Therefore, to further define the prevalence, frequency and characteristics of PVCs in normal subjects we performed 24-hour ambulatory electrocardiography on 101 subjects free of evident disease as verified by extensive noninvasive and invasive testing, including coronary arteriography.

Materials and Methods

Population

We studied 101 subjects in whom physical examination of the cardiovascular system, chest x-ray, ECG, maximal exercise stress test, echocardiogram, right- and left-heart catheterization and coronary arteriography were normal. Ninety-nine of these subjects were selected from 1500 patients referred for cardiac catheterization to the laboratories associated with CMDNJ-Rutgers Medical School for differential diagnosis of chest pain. Two subjects were studied because of hypercholesterolemia and strong family history of cardiac disease. Cardiac catheterization was performed by the Sones technique.15 Subjects with lesions of the coronary arteries compromising the lumen by only 5-10%, or with minor luminal irregularities were excluded. Single-plane ventriculography was performed in the right anterior oblique...
projection. Patients with abnormal left ventricular function as evidenced by an ejection fraction below 50%, end-diastolic pressure above 12 mm Hg, or localized contraction abnormalities were excluded. Patients with mitral valve prolapse diagnosed by ventriculography or echocardiography, valvular disease, abnormal right ventricular pressures, bundle branch block, ventricular hypertrophy, abnormal ST or T wave, or other abnormalities of the resting ECG were excluded. M-mode echocardiography was performed in all subjects. Subjects with abnormal chamber size, increased septal thickness and mitral valve prolapse were excluded. The subjects performed a maximal treadmill stress test using a Balke protocol. Fatigue or dyspnea was the end point in all subjects. Subjects who developed horizontal or downsloping ST depression more than 0.75 mm (0.075 mV) during or after exercise were excluded. Tests of blood sugar, blood urea nitrogen, serum creatinine, uric acid, total bilirubin, calcium, alkaline phosphatase, SGOT, cholesterol, triglycerides, total protein, albumin, LDH, sodium, potassium, chloride and CO₂, as well as a complete blood count and urinalysis, were performed. Significant extracardiac disease was excluded by these tests, history and physical examination. The height, weight and sex of the subjects and the use of coffee, tea, alcohol and tobacco were noted. The body mass index was calculated by dividing the weight by the square of the height. The mean, range and standard deviation of some of these variables are shown in Table 1.

There were 51 men and 50 women, mean age 48.8 ± 10 years (sd) (range 16–68 years). The chest pain that prompted the coronary arteriography was in retrospect attributed to extracardiac causes in 51 subjects. Chest wall disorders were diagnosed in 13, esophageal disease in 29 and cervical osteoarthritis in 19; psychological disturbances were thought to be the cause of pain in seven subjects.

### Ambulatory Electrocardiography

Ambulatory electrocardiography was performed for 24 hours using portable Avionics tape recorders (Model 445) to obtain two leads corresponding to a modified V₁ and V₈. Ambulatory electrocardiography for two additional 24-hour periods was performed on a random subset of 30 subjects. Satisfactory recordings covering at least 18 of the 24 hours were available on 99 subjects. The tapes were played back on a 660A Avionics playback system by an experienced nurse. All disturbances of the rhythm were written out on electrocardiographic paper at 25 mm/sec and verified by a cardiologist. To ascertain that a significant arrhythmia was not missed during playback, 1 hour of each recording and 10 24-hour complete recordings were played back at a paper speed of 5 mm/sec. Five PVCs (2.2%) were missed by the nurse. The PVCs were classified as having right ventricular morphology if the terminal QRS deflection was positive in modified lead V₄ and negative in modified lead V₈. PVCs with left ventricular morphology had a positive terminal QRS deflection in modified lead V₁ and a negative terminal QRS deflection in modified lead V₈. PVCs not meeting either criterion were considered unclassifiable. The prematurity index was calculated by dividing the coupling interval (RR') by the QT interval of the preceding normal beat. The aberration index was derived by dividing the QRS duration of the PVC by the QRS duration of the normal beats.

For each hour, the maximal and minimal heart rates, total beats/hour and the number of PVCs of each morphology were tabulated. The average heart rate was obtained by dividing the number of beats/hour by 60. The data were entered into an IBM 370/168 computer and analyzed statistically. Analyses included correlation coefficients using parametric and nonparametric techniques, cross-tabulations, chi-square, independence tests, and t tests. Each analysis was limited to cases without missing values for pertinent variables.

### Results

Thirty-nine of the 101 subjects had at least one PVC when monitored for 24 hours. However, the number of PVCs/24 hours was rather small. Table 2 shows the percentage of subjects that had a given number of PVCs when monitored for different time intervals. Four subjects had more than 100 PVCs/24 hours and only one had more than 500 in this time interval. Three subjects had more than five PVCs in any given hour. The percentage of subjects who did not have any PVCs during monitoring decreased when recordings longer than 1 day were used. When 2 days of recording were analyzed, 10 of 30 subjects (33%) did not

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### Table 1. Range, Mean and Standard Deviation of Selected Variables in Subjects with Normal Hearts

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean</th>
<th>Max</th>
<th>Min</th>
<th>sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.8</td>
<td>68</td>
<td>16</td>
<td>10.0</td>
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<tr>
<td>Weight (lbs)</td>
<td>164.7</td>
<td>250</td>
<td>94</td>
<td>32.4</td>
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<tr>
<td>Height (inches)</td>
<td>66.9</td>
<td>74</td>
<td>59</td>
<td>3.9</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>148.9</td>
<td>720</td>
<td>32</td>
<td>108.9</td>
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<tr>
<td>Cholesterol (mg/dl)</td>
<td>218.1</td>
<td>480</td>
<td>120</td>
<td>55.8</td>
</tr>
<tr>
<td>K⁺ (mEq/l)</td>
<td>4.3</td>
<td>5.8</td>
<td>3.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Na⁺ (mEq/l)</td>
<td>141.2</td>
<td>158</td>
<td>130</td>
<td>5.9</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>14.2</td>
<td>16.9</td>
<td>11.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.6</td>
<td>10.0</td>
<td>3.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.5</td>
<td>11.2</td>
<td>7.8</td>
<td>0.6</td>
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<tr>
<td>Maximal BP (mm Hg)</td>
<td>129.4</td>
<td>200</td>
<td>100</td>
<td>20.1</td>
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<tr>
<td>Minimal BP (mm Hg)</td>
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<td>110</td>
<td>50</td>
<td>11.8</td>
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<tr>
<td>Cigarettes/day</td>
<td>8.5</td>
<td>80</td>
<td>0</td>
<td>15.5</td>
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<tr>
<td>Coffee (cups per day)</td>
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<td>14</td>
<td>0</td>
<td>3.0</td>
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<tr>
<td>Body mass index (100 × lbs/ft²)</td>
<td>0.4</td>
<td>5.3</td>
<td>3.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Alcohol (½ oz/week)</td>
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<td>84</td>
<td>0</td>
<td>11.6</td>
</tr>
<tr>
<td>Glucose</td>
<td>100.2</td>
<td>173</td>
<td>75</td>
<td>17.2</td>
</tr>
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</table>
have any PVCs and only five of 30 (17%) did not have any PVCs in 3 days. The percentage of subjects who had a given number of PVCs/24 hours after 1, 2 and 3 days of recording is shown in figure 1. The distribution is unimodal and tends to assume a normal configuration with increasing number of days of tape recording. The occurrence of PVCs varied considerably in successive 24-hour recordings. Of the 17 subjects who did not have PVCs in the first 24-hour recording, 10 did not have PVCs in two 24-hour recordings and five did not have PVCs in any of the three 24-hour recordings. Of the 13 subjects who had at least one PVC in the first recording, four did not have any PVCs in a repeat recording.

With increasing age, the number of PVCs recorded in 24 hours increased significantly. The (nonparametric) Spearman’s rank correlation coefficient was 0.33 (p = 0.001) and the Pearson product-moment correlation coefficient was 0.19 (p = 0.067). The probability of having more than 1, more than 50, and more than 100 PVCs/24 hours in different age groups is shown in table 3. The probability of having at least 1 PVC/24 hours also increased with age (chi-square = 11.789, p = 0.019).

No significant association of the presence or absence of PVCs or the number of PVCs/24 hours and other variables (sex, systolic blood pressure, glucose, weight, height, body mass index, serum cholesterol, triglycerides, uric acid, potassium and calcium, blood hemoglobin, the ingestion of coffee, tea or alcohol and cigarette smoking) was noted. No consistent relationship between the heart rate and the occurrence of PVCs was found, although a positive correlation (r = 0.61) between the number of PVCs/hour and the maximal heart rate in the same hour was seen in one patient. A diurnal pattern of the occurrence of PVCs could not be identified.

Complex forms of ventricular ectopy were rare. Multiform PVCs (bifocal) occurred in four subjects. Two of these subjects in addition had early PVCs (prematurity index less than 1.0). PVCs with prematurity index less than 0.9 were not observed. Three subjects had brief periods of bigeminy. No subject had two or more PVCs in a row.

The distribution of the prematurity index is shown in figure 2. In this analysis all subjects who had PVCs either in the first 24-hour recording (39 subjects) or in repeat recordings performed in a random subset of 30 (12 additional subjects) are included. The mode is in the interval between 1.21 and 1.40, the mean is 1.41 and the standard deviation is 0.37. The range of pre-
maturity index is 0.9–2.63. The aberration index (QRS duration of PVC/QRS duration of normal beat) had a mode between 1.81 and 2.10, a mean of 1.84, a standard deviation of 0.37 and a range of 1.2–3.0. The QRS duration of the PVC had a mode between 0.11 and 0.13 second, a range of 0.09–0.2 second, a mean of 0.129 second and a standard deviation of 0.028 second (fig. 3). Four subjects had PVCs with duration longer than 0.16 second. Among the 51 subjects with PVCs, 25 had PVCs of right ventricular morphology, 15 had PVCs of left ventricular morphology and four had PVCs both of right and left ventricular morphology. In seven subjects the origin could not be ascertained from the two monitored electrocardiographic leads.

Discussion

This study shows that the majority of subjects with normal hearts have a small number of PVCs. Only 5% of the subjects had more than five PVCs in any given hour and 4% had more than 100 PVCs/24 hours. These findings are similar to those of Brodsky and associates in a younger age group. The number of PVCs in subjects with normal hearts in this study is lower than that reported by Clarke et al., who studied apparently normal subjects, and by Hinkle et al. Persons with undetected or known heart disease, especially coronary artery disease, may have been included in these studies and may account for the higher incidence of PVCs.

Because the subjects in this study were catheterized before they entered the study, the condition that led to cardiac catheterization might have caused some of the arrhythmias reported here. This is unlikely for several reasons. A meticulous search for cardiac disease was performed by noninvasive and invasive methods. Coronary artery disease was excluded by coronary arteriography, and patients with even minor abnormalities of the coronary arteriogram were excluded from the study. Asymmetric septal hypertrophy and mitral valve prolapse were excluded by cardiac catheterization, ventriculography and echocardiography. Valvular disease and congestive cardiomyopathy were excluded by ventriculography and cardiac catheterization, and Prinzmetal's angina with normal coronary arteriography was excluded by ambulatory electrocardiography. Patients with the syndrome of chest pain and an abnormal stress test were excluded by the normal findings on maximal exercise stress test. Therefore, it is unlikely that these subjects have any known cardiac disease.

Serious extracardiac disease was excluded as the cause of PVCs because the history, physical examination, chest x-ray and biochemical screen failed to disclose significant systemic disease.

The cause of pain that led to cardiac catheterization was not related to the presence or number of PVCs. For example, the subjects in whom the pain was attributed to esophageal disease did not have a

Figure 2. Frequency distribution of prematurity index of premature ventricular complexes recorded in 51 subjects with normal hearts.

Figure 3. Frequency distribution of the duration of premature ventricular complexes (PVCs) in 51 subjects with normal hearts.
significantly different number of PVCs from subjects in whom the pain was not attributed to esophageal disease (t = 0.79, p = 0.43). Similar results were found when other causes of chest pain, i.e., cervical osteoarthritis (t = 0.52, p = 0.17), chest wall disorder (t = 0.039, p = 0.97), and psychological abnormality (t = 0.527, p = 0.61) were studied. These considerations and the smaller incidence and frequency of PVCs than reported in apparently normal subjects indicate that the data reported here pertain to normal subjects. Patients who presented with PVCs or palpitations were excluded from the study. As some of these patients have normal hearts, the incidence of PVCs in normal subjects may be higher than that reported here.

Several investigators have found that the incidence and frequency of PVCs increases with age in apparently normal subjects. The explanation is that undetected coronary artery disease becomes more prevalent with increasing age and results in an increase of the incidence and frequency of PVCs. In this study the incidence and frequency of PVCs were increased with increasing age, although coronary artery disease was excluded by coronary arteriography. Therefore, a different explanation must be sought. We speculate that degenerative changes of the myocardium that increase with age, or small scars resulting from overt or subclinical transient myocarditis, may cause PVCs.

Increased systolic blood pressure has been associated with PVCs in a large population. In this study, the PVCs in subjects with high systolic blood pressure could have been caused by left ventricular hypertrophy secondary to the elevated blood pressure. Subjects with left ventricular hypertrophy were excluded from our study by echocardiography and electrocardiography, and PVCs were not associated with high blood pressure. Using coronary arteriography, we also excluded subjects with coronary atherosclerosis, a more prevalent cause of PVCs in subjects with high systolic blood pressure.

Frequent and complex ventricular irritability has been reported in subjects with normal hearts as diagnosed by extensive noninvasive and invasive testing. This finding is not in direct contradiction with our findings because normal subjects with frequent PVCs may represent the extreme of the distribution of normal subjects (i.e., frequent PVCs may occur extremely rarely in normal subjects). Alternately, these subjects may suffer from a form of cardiac disease that has not yet been identified. One can easily imagine that subjects with mitral valve prolapse and PVCs would have been classified as normal before the recognition of this syndrome.

During prolonged ambulatory monitoring (3 days), the distribution of subjects according to the number of PVCs is unimodal and approaches the normal curve, suggesting that PVC of low frequency are not necessarily a manifestation of disease, and that with prolonged monitoring, PVCs can be identified in the majority of normal subjects.

Bimodal distributions suggesting that there were two types of subjects, one with low and one with high frequency of PVCs (probably one with healthy and one with diseased hearts), were observed in previous studies of subjects in whom cardiac disease was not excluded. This conforms to the common observation that practically all persons of middle or advanced age have experienced occasional PVCs.

PVCs detected in this population were more often of right than left ventricular morphology. Twenty-five of 51 subjects with PVCs (39 with PVCs in the first 24 hour recording and 12 with PVCs only in a repeat recording) had PVCs of right ventricular morphology and only 15 had PVCs of left ventricular morphology. This tendency of normal subjects to have right ventricular PVCs has been reported, and an adequate explanation for it is not known. It is reasonable to expect that patients with disease of the left ventricle would have PVCs originating in that ventricle. However, the reason for the increased frequency of right ventricular PVCs in normal subjects is not apparent. This study indicates that the predilection of normal subjects to have PVCs of right ventricular morphology is not absolute and that many normal subjects have PVCs of left ventricular morphology. In addition, the electrocardiographic configuration of PVCs depends not only on the focus of origin of the arrhythmia, but also on the site of exit, which may be in either ventricle. Therefore, the electrocardiographic morphology of the PVC is not a reliable indicator of the presence or absence of cardiac disease. Complex forms of ventricular ectopy that carry serious prognostic implications in patients with ischemic heart disease (e.g. PVCs interrupting the T wave, multiform PVCs, and salvos) were rare. Only four subjects had multiform PVCs, two of whom had early PVCs. Increased QRS duration of the PVC (> 0.16 second) has also been associated with heart disease. In our study, only four of 101 subjects had PVCs longer than 0.16 second. Considerable day-to-day variation in the occurrence of PVCs was observed. Similar variations of the frequency of PVCs in patients with heart disease have been reported.

We did not find a significant correlation between the presence and frequency of PVCs and variables that have been associated with PVCs in previous reports (e.g., hypokalemia and use of coffee or alcohol). PVCs have been reported in subjects with marked hypokalemia and are evident in subjects with alcoholic cardiomyopathy, and occasionally in subjects without alcoholic cardiomyopathy who consume alcohol. The lack of correlation between PVCs and these variables in our study is probably because the potassium, sodium, hemoglobin, uric acid, and other variables we studied did not show extreme deviations from the normal, and only a few subjects consumed large amounts of alcohol and coffee (table 1).

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References

Premature ventricular complexes in the absence of identifiable heart disease.
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