Predictive Implications of Ventricular Premature Contractions Associated with Treadmill Stress Testing

JOHN A. UDALL, M.D., AND MYRVIN H. ELLESTAD, M.D.

SUMMARY Follow-up data on future coronary events was collected on 6,500 patients who had undergone stress testing; 1,327 of these exhibited ventricular premature contractions (VPCs) associated with one or more phases of treadmill stress testing (TSTs). Eighty-three percent of all patients tested had known or suspected cardiovascular disease. The annual incidence of new coronary events (myocardial infarction, angina, cardiac death) during a five year follow-up was 1.7% among 1,067 patients without VPCs or ischemic ST changes, 6.4% in 758 patients with VPCs alone, 9.5% among 609 patients with ischemic ST changes alone and 11.4% in 569 patients with VPCs plus ischemic ST changes. The significance of VPCs associated with the TSTs rests largely upon the clinical status of the persons tested. VPCs observed among patients referred for TSTs for the evaluation of known or suspected cardiovascular disease, with or without ischemic ST abnormalities, represent a definite risk factor for future coronary events.

THE SIGNIFICANCE OF VENTRICULAR PREMATURE CONTRACTIONS (VPCs) occurring at rest and with exercise remains controversial in the differentiation of cardiac patients from healthy people. McHenry and Froelicher and associates\(^1\) reported recently upon the failure of exercise-induced VPCs to identify patients with heart disease among select populations of actively employed policemen and airmen, respectively. The present study was undertaken to determine the incidence of future coronary events by analyzing follow-up data up to five years among another select group, 1,327 patients referred to a major medical center for treadmill stress testing (TST) who exhibited VPCs at rest, during, or after exercise.

Methods and Materials

Follow-up information on 6,500 patients stress tested at the Long Beach Memorial Hospital Medical Center since 1964 was obtained by trained technicians and fellows in cardiology by patient interviews or from referring doctors' records. A single follow-up was made on each patient at an interval between 6 and 60 months after the TST. Because increasing numbers of tests have been performed during the past 24 months, the patient sample is much larger during that period as compared to the first three years. There were no patients lost to follow-up. Among 1,327 patients, VPCs were observed in association with one or more of the 3 phases of treadmill testing; at rest and hyperventilation, during exercise and/or during the recovery period. All patients (1,327) who exhibited one or more VPCs during one or more phases of the TST were included in the analyses. The number of VPCs identified during each phase was estimated as a ratio to normal sinus beats. By this method, it was possible to determine quite accurately which patients showed an increase or decrease during exercise and recovery.

New coronary events were identified and defined as a myocardial infarction, the onset or progression of angina, or a death due to a cardiac cause. Infarctions were established by typical symptoms, supported by electrocardiographic and/or enzyme changes. Onset of angina was determined by the referring doctor's chart notations and the administration of nitroglycerin. Progression of angina was identified by decreased exercise tolerance because of chest pain and/or increased amounts of anti-anginal medication prescribed. Deaths due to a cardiac cause were defined as those immediately following myocardial infarction or cardiac failure and those occurring suddenly leading to a conclusion of cardiac arrest.

The study population of 6,500 was composed of approximately 80% men and 20% women. Racial and ethnic differences were not identified. Most patients were referred for the evaluation of chest pain (57%), history of myocardial infarction (22%), high blood pressure (22%), or previous cardiac surgery (6%). Only 17% of those studied were free of known or suspected cardiovascular disease as determined by a comprehensive pre-test questionnaire. Treatment received was not taken into consideration in the follow-up study of coronary events which extended from 6 months to 5 years. These events were analyzed by the life table method of Cutler and Ederer\(^3\). Treadmill stress testing (TST) was performed according to a protocol described previously\(^4\) with continuous monitoring until an age-adjusted maximum predicted pulse rate was reached. Positive TSTs with regard to ischemic ST abnormalities were defined as 1 mm of depression or elevation lasting 80 milliseconds or more from the J point during or after exercise. Patients receiving digitalis, those with unstable angina, and those with ST abnormalities at rest were excluded from the analyses. Early termination of the TST was often necessitated by the appearance of angina, severe ischemic ST changes, complete exhaustion, or serious arrhythmias; for example, frequent multiform VPCs, ventricular bigeminy and tachycardia. Moderate numbers of unifocal VPCs, well removed from preceding T waves, were observed closely without aborting the test. All patients exhibiting one or more VPC at rest during or after TST were included in the analyses. Differences were analyzed statistically by the Chi square method.

Future coronary events were compared between 758 patients who exhibited VPCs alone and the remaining 569...
who manifested VPCs plus ischemic ST abnormalities. Additional comparisons were made among 1,067 patients who exhibited neither VPCs nor ischemic ST changes, plus 609 patients with ischemic ST changes but no VPCs during exercise reported earlier from this hospital from the same cohort\(^\text{a}\) and the 1,327 patients comprising the present report. A comparison was also made of a single coronary event, deaths due to a cardiac cause, among patients with VPCs and negative TSTs and patients with VPCs and positive TSTs.

"Ominous" VPCs, defined as multifocal, bigeminal, repetitive and ventricular tachycardia, were observed in 201 patients. These were analyzed separately with regard to subsequent coronary events and the results compared with those obtained from the remaining patients manifesting less serious ventricular premature contractions. In addition, future coronary events among 123 patients who exhibited VPCs which increased during TSTs were compared among 1,230 patients with VPCs at rest and/or during exercise which did not increase during stress testing. Finally, the ages of all patients with and without VPCs were compared by the percentages found in each decade.

**Results**

**Combined Coronary Events**

Of the 6,500 patients tested, 1,327 (20%) exhibited VPCs before, during, or after exercise. The incidence of one or more future coronary events among 758 patients with VPCs and negative TSTs equalled 6.4% annually (fig. 1, table 1). This contrasts sharply with an annual incidence of 1.7% among 1,067 patients without VPCs or ischemic ST changes from the same cohort \(P < 0.001\). Future coronary events among 569 patients with VPCs and positive TSTs averaged 11.4% annually. Table 1 reveals a progressive increase in subsequent coronary events among patients referred for TSTs who exhibit VPCs only, ischemic ST changes without VPCs, and ischemic ST changes plus VPCs. Thus the appearance of VPCs during TSTs, with or without associated ST changes, has an important predictive implication of future coronary events among patients referred to a major medical center with known or suspected cardiovascular disease.

**Deaths**

Deaths due to cardiac causes over five years were also significantly higher among the 758 patients with VPCs and negative TSTs (8%) compared to the 1,067 patients without VPCs or ischemic ST changes (1.4%) \(P < 0.001\). Not surprisingly, cardiac deaths were much higher among the 569 patients with VPCs and positive TSTs (22%) (fig. 2).

Among patients with ominous VPCs and negative TSTs, the incidence of future coronary events during the first year of follow-up was approximately twice (29%) that observed among similar patients with negative TSTs but less frequent unifocal VPCs (15%) \(P < 0.01\) (table 2). Patients with ominous VPCs and positive TSTs also showed a significantly higher incidence of future coronary events during the first year (42%) compared to similar patients with positive TSTs but less frequent unifocal VPCs (33%) \(P < 0.05\) (table 3).

Among patients with VPCs which increased during exercise there were significantly more coronary events during the first two years after TSTs (42%) than among patients with VPCs at rest and/or during exercise which did not increase with progressive physical stress (24%) \(P < 0.001\) (table 4). The incidence of coronary events among patients with VPCs which decreased or disappeared during exercise was not significantly different compared to patients with VPCs at rest and/or during exercise which did not change.

An age comparison was made between patients with and without VPCs to evaluate the possibility that patients with VPCs might have been much older as a group and more

**Table 1. The Annual Incidence of Coronary Events Among Patients with Negative and Positive Exercise Tests, with and without Ventricular Premature Contractions**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Coronary Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative TSTs and no VPCs</td>
<td>1067</td>
</tr>
<tr>
<td>Negative TSTs and VPCs</td>
<td>758</td>
</tr>
<tr>
<td>Positive TSTs and no VPCs</td>
<td>609</td>
</tr>
<tr>
<td>Positive TSTs and VPCs</td>
<td>569</td>
</tr>
</tbody>
</table>

\*From reference 5.

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**Figure 1.** Coronary events related to development of ventricular premature contractions (VP) and stress testing. Myocardial infarction, onset or progression of angina, death due to a cardiac cause comprise the events monitored. The percentages indicate those subjects not having an event each year. The vertical lines indicate two standard deviations of the mean. When these limits do not overlap, the results for each group are significantly different \(P < 0.01\) by Chi square analysis. A) Coronary events among patients with ventricular premature contractions and negative exercise tests. B) Coronary events among patients with ventricular premature contractions and positive exercise tests.
VPCs during exercise testing/udall, ellestad

Decompressing numbers analyzed each year represent fewer patients with long intervals between TSTs and follow-up. There were no patients “lost to follow-up.”

Figure 2. Deaths due to a cardiac cause. The percentages indicate those subjects surviving each year. The vertical lines indicate two standard deviations of the mean. When these limits do not overlap, the results for each group are significantly different (P < 0.01) by Chi square analysis. A) Cardiac deaths among patients with ventricular premature contractions and negative exercise tests. B) Cardiac deaths among patients with ventricular premature contractions and positive exercise tests.

prone to coronary events than younger people without VPCs. VPCs did occur in higher percentages among patients in the older three decades (51 to 80 years) compared to patients without; however, the differences proved to be small between the two groups (Table 5). A preponderance among older people was found to parallel earlier reports 6, 7 which have documented a progressive increase in the incidence and frequency of VPCs with aging. These results refute the hypothesis that patients with VPCs in the present study were

Table 2. The Annual Incidence of Coronary Events among Patients with Negative Exercise Tests and Infrequent Ventricular Premature Contractions Compared to Those with Ominous Ventricular Premature Contractions

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Events</td>
</tr>
<tr>
<td>A. Infrequent Unifocal VPCs</td>
<td></td>
</tr>
<tr>
<td>At Rest</td>
<td>182</td>
</tr>
<tr>
<td>During Exercise</td>
<td>504</td>
</tr>
<tr>
<td>Recovery (ave.)</td>
<td>461</td>
</tr>
<tr>
<td>B. “Ominous” VPCs</td>
<td>73</td>
</tr>
</tbody>
</table>

Table 3. The Annual Incidence of Coronary Events among Patients with Positive Exercise Tests and Infrequent Ventricular Premature Contractions Compared to Those with Ominous Ventricular Premature Contractions

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Events</td>
</tr>
<tr>
<td>A. Infrequent Unifocal VPCs</td>
<td></td>
</tr>
<tr>
<td>At Rest</td>
<td>187</td>
</tr>
<tr>
<td>During Exercise</td>
<td>435</td>
</tr>
<tr>
<td>After Exercise (ave.)</td>
<td>452</td>
</tr>
<tr>
<td>B. “Ominous” VPCs</td>
<td>128</td>
</tr>
</tbody>
</table>

much older and coronary-prone, and by inference, advanced age might have been responsible for the greater incidence of coronary events among patients who exhibited VPCs.

Coronary events were observed much more frequently during the first year after TSTs compared to subsequent years of observation. Almost half of all such events occurred during the first year after stress testing; 15% versus 32% during all five years among patients with VPCs alone. The same trend obtained among the remainder who exhibited VPCs plus ischemic ST changes; 32% during the first year compared to 57% during the 5 years of follow-up (fig. 1).

Discussion
Since Bourne 4 first reported half a century ago an association between coronary sclerosis and VPCs which increase with exercise, their significance has been investigated extensively but is not yet clearly defined. It is generally agreed that 1) VPCs increase with aging 6, 7 and occur commonly in both healthy people and cardiac patients 1, 2, 6 2) VPCs which decrease or disappear with exercise suggest a benign etiology, but this response cannot be relied upon to exclude organic heart disease 10-13 3) VPCs which increase with exercise suggest underlying heart disease, 12-14 most commonly coronary heart disease in this country, 11 and 4) VPCs which are very frequent, multiform, and/or sequential suggest coronary heart disease of a severe degree 12-14 which may be in an acute or unstable phase. 4

A fifth area of agreement is emerging regarding VPCs which occur during treadmill stress tests; their significance rests largely upon the clinical status of the subjects, or patients, as the case may be, tested. Among subjects tested routinely who are apparently healthy, VPCs have not proved useful indicators of organic heart disease 1, 10, 15 or future cor-

Table 4. The Annual Incidence of Coronary Events among Patients with Ventricular Premature Contractions at Rest, During Exercise, Increased and Decreased During Exercise

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Events</td>
</tr>
<tr>
<td>A. VPCs at rest</td>
<td>314</td>
</tr>
<tr>
<td>B. VPCs during exercise</td>
<td>916</td>
</tr>
<tr>
<td>C. VPCs increased during exercise</td>
<td>123</td>
</tr>
<tr>
<td>D. VPCs decreased or disappeared during exercise</td>
<td>92</td>
</tr>
</tbody>
</table>
Table 5. The Percentage of Patients in Each Decade Among all 6,500 Studied with and without Ventricular Premature Contractions

<table>
<thead>
<tr>
<th>Ages by decades</th>
<th>Patients with VPCs (21% of the total)</th>
<th>Patients without VPCs (79% of the total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-30</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>31-40</td>
<td>12%</td>
<td>19%</td>
</tr>
<tr>
<td>41-50</td>
<td>34%</td>
<td>38%</td>
</tr>
<tr>
<td>51-60</td>
<td>36%</td>
<td>28%</td>
</tr>
<tr>
<td>61-70</td>
<td>11%</td>
<td>7%</td>
</tr>
<tr>
<td>71-80</td>
<td>3%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Coronary events. By contrast, VPCs observed in association with TSTs among patients with known or suspected cardiovascular disease support the diagnosis of heart disease and those occurring among patients with chest pain, hypertension, and/or myocardial infarctions are definitely harbingers of future coronary events.

Healthy Subjects

Lamb and Hiss reported the influence of exercise on VPCs among 2,160 healthy subjects in 1962 and concluded that VPCs had no clinical significance in this population, occurring more by chance than precipitated by exercise. Gooch reached a similar conclusion from a review of the results of 3,000 stress tests 10 years earlier. Simultaneously, McHenry et al. reported a surprisingly high incidence of VPCs among a third of 650 policemen during routine TSTs and found the incidence was not significantly higher among 89 policemen with known or suspected cardiovascular disease compared to the remaining 561 considered to be free of heart disease. They concluded in general that VPCs did not differentiate the two groups. Shortly thereafter, Froelicher et al. reported the same high incidence (35%) of VPCs during TSTs among 1,390 active-duty airmen. These asymptomatic subjects were followed for an average of 6.3 years and VPCs proved not to be practical markers of increased risk of coronary artery disease in this population, except when associated with abnormal ST segment responses. Sandberg reached the same conclusion, citing the decisive factor in the TST result to be whether or not VPCs which may occur are accompanied by an ischemic ST segment response.

Cardiac Patients

The implications of VPCs during TSTs among patients with known or suspected cardiovascular disease, with or without ischemic ST changes, are substantial. Mann and Burchell found evidence of arteriosclerotic heart disease among 11 consecutive patients who exhibited VPCs during the recovery period of exercise testing. Among 38 patients evaluated for chest pain who exhibited exercise-induced VPCs, Helfant et al. identified 22 with coronary disease, 10 with cardiomyopathy, and only 6 were normal by cardiac catheterization and coronary angiography. Zaret and Conti found coronary arteriosclerosis by angiography in 23 of 32 patients (72%) who experienced exercise-induced ventricular irritability. Eighteen of the 23 exhibited ischemic ST abnormalities as well. They also reported more severe double and triple coronary obstructive disease among patients with exercise-induced VPCs compared to a similar group of patients with coronary arteriosclerosis who did not generate VPCs during TSTs. Goldschlager et al. reported similar results from their study of 170 patients with coronary artery disease; 81 with VPCs during TSTs exhibited more advanced obstructive arteriosclerosis and severe left ventricular dysfunction by heart catheterization, and also more prior myocardial infarctions, compared to the remainder who did not exhibit exercise-induced VPCs.

The results of the present study involving 1,327 patients with known or suspected cardiovascular disease, 57% treadmill tested to evaluate chest pain, corroborate the reports cited above. Ventricular premature contractions occurring in this select population, with or without ischemic ST abnormalities, were definitely markers of future coronary events at a risk more than 4 times greater compared to patients in this same cohort who did not exhibit VPCs (table 1). Thus a fifth general concept regarding VPCs is gaining validity; the significance of VPCs associated with TSTs rests largely upon the clinical status of the persons being studied. VPCs observed among healthy subjects tested routinely are very common and are not reliable indicators of heart disease or future coronary events unless associated with ischemic ST abnormalities. On the other hand, VPCs occurring among patients referred for TSTs with known or suspected cardiovascular disease, with or without associated ischemic ST changes, represent a definite risk factor for future coronary events.

Patients who exhibit VPCs plus ischemic ST changes experience a higher incidence of future coronary events compared to others who demonstrate only VPCs or ischemic ST changes alone. Thus, the risk of coronary events appears to ascend progressively among patients referred for TSTs who exhibit VPCs alone (6.4%/year), ischemic ST changes alone (9.5%/year), and VPCs plus ischemic ST changes together (11.4%/year) (table 1). In addition, patients with either negative or positive TSTs who exhibit ominous VPCs experience a significantly increased incidence of future coronary events compared to others in each category with less frequent unifocal VPCs (tables 2 and 3).

Time Relationships Between a Decision for Stress Testing, Ventricular Premature Contractions, and Future Coronary Events

The incidence of future coronary events among all referred patients with exercise-induced VPCs proved to be twice as great during the first year as compared to the subsequent four years of follow-up, both among patients with and without ischemic ST abnormalities (fig. 1). This observation was somewhat unexpected and prompted a conclusion that a sequential relationship may exist between the onset or progression of chest pain in a given patient, a decision for a TST shortly thereafter, coronary circulatory instability at this particular time, and a very significant risk of a coronary event during the year ahead among those who exhibit VPCs. Thus, it would appear that we are dealing not only with a select population referred for TSTs, but these patients are encountered at a strategic time in their lives, shortly after they consulted a physician who made a decision to order a TST. Among these highly selected patients, those who exhibit VPCs during TSTs are faced with a very substantial risk of one or more coronary events during the year immediately ahead.
The results of the present study support the generally accepted concepts regarding VPCs. They occur commonly among cardiac patients, increase with age, suggest underlying heart disease when they increase with exercise, and suggest an acute or unstable phase of organic heart disease when they are ominous (very frequent, multifocal and/or sequential). Ventricular premature contractions which decrease or disappear during TSTs among patients with known or suspected heart disease share the same predictive implications with VPCs which are sustained during exercise.

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References

The Influence of Constitutional Variables on Orthogonal Electrocardiograms of Normal Women

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JOSEPH T. DOYLE, M.D., AND HUBERT V. PIPBERGER, M.D.

SUMMARY Correlations between 276 orthogonal electrocardiographic measurements and constitutional variables were made in 450 normal women, aged 18 to 90 years.
Advancing age led to decreases in amplitudes, left QRS axis shift, rightward and superior displacement of the ST segment, and anterior shift of the T wave. QRS amplitude was absent in 1% of normal women over age 40. In the oldest subjects, R amplitude was 71% and R, amplitude was 80% of the respective values in the youngest group. Whereas QRS amplitude decreases with age levelled off at the sixth decade of life, they continued to old age for ST-T measurements. Men revealed steeper age trends than women. Blacks had larger QRS amplitudes and smaller Q/R ratios than whites.

RELIANCE ON THE ELECTROCARDIOGRAM (ECG) for objective documentation of cardiovascular disease requires determination of accurate normal limits. Constitutional variables are known to exert a major influence upon such limits and significantly affect ECG interpretations.

Extensive cross-sectional studies on conventional 12-lead ECGs reported by Simonson and several longitudinal and epidemiological studies clearly demonstrated that ranges of normal may be considerably reduced by incorporation of information on constitutional variables such as age, sex, race, and body weight. Narrower ranges, by minimizing the overlap between normal and abnormal, should result in a substantial improvement in diagnostic ECG classification and interpretation.

In the present report, extensive correlations are described between Frank-lead ECGs obtained from 450 normal women and the following constitutional variables: age, race, weight, height, and chest configuration. The results are com-

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